AMENDMENTS

IN THE SPECIFICATION:

Please enter the specification amendments as follows.

Beginning on page 2, line7 and ending on page 3, line 19:

A1

Cell adhesion occurs through a coordinately regulated series of steps that allow the leukocytes to first adhere to a specific region of the vascular endothelium and then cross the endothelial barrier to migrate to the inflamed tissue (Springer, T.A., 1994, "Traffic Signals for Lymphocyte Recirculation and Leukocyte Emigration: The Multistep Paradigm," Cell 76: 301-314; Lawrence, M. B., and Springer, T. A., 1991, "Leukocytes Roll on a Selectin at Physiologic Flow Rates: Distinction from and Prerequisite for Adhesion Through Integrins," Cell 65: 859-873; von Adrian, U., Chambers, J. D., McEnvoy, L.M., Bargatze, R.F., Arfos, K.E, and Butcher, E.C., 1991, "Two-Step Model of Leukocyte-Endothelial Cell Interactions in Inflammation," Proc. Natl. Acad. Sci. USA 88: 7538-7542; and Ley, K., Gaehtgens, P., Fennie, C., Singer, M.S., Lasky, L.H. and Rosen, S.D.,1991, "Lectin-Like Cell Adhesion Molecule 1 Mediates Rolling in Mesenteric Venules *In Vivo*," Blood 77: 2553-2555). These steps are mediated by families of adhesion molecules such as integrins, Ig supergene family members, and selectins which are expressed on the surface of the circulating leukocytes and on the vascular endothelial cells. The first step consists of leukocytes rolling along the vascular endothelial cell lining in the region of inflammation. The rolling step is mediated by an interaction between a leukocyte surface oligosaccharide, such as Sialylated Lewis-X antigen (SLe^X), and a selectin molecule expressed on the surface of the endothelial cell in the region of inflammation. The selectin molecule is not normally expressed on the surface of endothelial cells but rather is induced by the action of inflammatory mediators such as TNF-α and interleukin-1. Rolling decreases the velocity of the circulating leukocytes in the region of inflammation and allows the cells to more firmly adhere to the endothelial cell. The firm adhesion is accomplished by the interaction of integrin molecules that are present on the surface of the rolling leukocytes and their counter-receptors (the Ig superfamily molecules) on the surface of the endothelial cell. The Ig superfamily molecules or CAMs (Cell Adhesion Molecules) are either not expressed or are expressed at low levels on normal vascular endothelial cells. The CAMs, like the

selectins, are induced by the action of inflammatory mediators like TNF-alpha and IL-1. The final event in the adhesion process is the extravasation of leukocytes through the endothelial cell barrier and their migration along a chemotactic gradient to the site of inflammation. This transmigration is mediated by the conversion of the leukocyte integrin from a low avidity state to a high avidity state. The adhesion process relies on the induced expression of selectins and CAMs on the surface of vascular endothelial cells to mediate the rolling and firm adhesion of leukocytes to the vascular endothelium.

A1

Beginning on page 4, line 6 and ending on page 4, line 20:

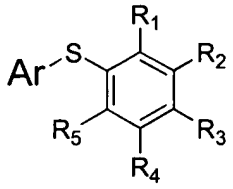
The present application discloses compounds which bind to the interaction-domain (I-domain) of LFA-1, thus interrupting endothelial cell-leukocyte adhesion by blocking the interaction of LFA-1 with ICAM-1, ICAM-3, and other adhesion molecules. These compounds are useful for the treatment or prophylaxis of diseases in which leukocyte trafficking plays a role, notably acute and chronic inflammatory diseases, autoimmune diseases, tumor metastasis, allograft rejection, and reperfusion injury. The compounds of this invention are diaryl sulfides, which are substituted with a cinnamide moiety. The cinnamide functionality may be placed either ortho- or para- to the linking sulfur atom, although para-substitution is preferable. Appropriate substitution of both aromatic rings is tolerated, and can be used to modulate a variety of biochemical, physicochemical and pharmacokinetic properties. In particular the amide moiety is readily modified; a variety of secondary and tertiary amides are active, and alternatively a heterocyclic ring may be attached at this position. Modifications of this amide functionality are particularly useful in modulating physicochemical and pharmacokinetic properties.

A2

Beginning on page 5, line 1 and ending on page 10, line 20:

Summary of the Invention

The present application provides compounds of formula **I**, below,



I

or a pharmaceutically-acceptable salt or prodrug thereof,

where R_1, R_2, R_3, R_4, and R_5 are each independently selected from

a. hydrogen,

b. halogen,

c. alkyl,

d. haloalkyl,

e. alkoxy,

f. cyano,

g. nitro,

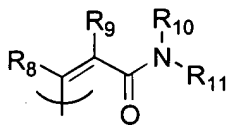
h. carboxaldehyde,

i. heterocyclylsulfanyl,

j. "*cis*-cinnamide", and

k. "*trans*-cinnamide",

where R_1 and R_3 are defined as



"*cis*-cinnamide"

"*trans*-cinnamide",

where R_8 and R_9 are each independently selected from

a. hydrogen,

b. alkyl,

c. carboxy alkyl,

d. monoalkylaminocarbonyl alkyl, and

e. dialkylaminocarbonyl alkyl,

and R_{10} and R_{11} are each independently selected from

a. hydrogen,

b. alkyl,

c. cycloalkyl,

d. alkoxycarbonylalkyl,

e. hydroxyalkyl,

f. substituted aryl,

A3

g. unsubstituted heterocyclyl,

h. unsubstituted heterocyclylalkyl,

i. heterocyclylamino,

j. substituted heterocyclyl,

k. substituted heterocyclylalkyl,

l. unsubstituted aryl,

m. arylalkyl,

n. carboxyalkyl, and

o. alkoxyalkyl,

or R_{10} and R_{11} are taken together with N to form an unsubstituted heterocyclyl or substituted heterocyclyl group, substituted by one or more than one substituent, each substitutent independently selected from

1) alkyl

2) alkoxy,

3) alkoxyalkyl,

4) cycloalkyl,

5) aryl,

6) heterocyclyl,

7) heterocyclylcarbonyl,
8) heterocyclylalkylaminocarbonyl,
9) hydroxy,
10) hydroxyalkyl,
11) hydroxyalkoxyalkyl,
12) carboxy,
13) carboxyalkyl,
14) carboxycarbonyl,
15) carboxaldehyde,
16) alkoxycarbonyl,
17) arylalkoxycarbonyl,
18) aminoalkyl,
19) aminoalkanoyl,
20) carboxamido,
21) alkoxycarbonylalkyl,
22) carboxamidoalkyl,
23) cyano,
24) unsubstituted tetrazolyl,
25) substituted tetrazolyl,
26) alkanoyl,
27) hydroxyalkanoyl,
28) alkanoyloxy,
29) alkanoylamino,
30) alkanoyloxyalkyl,
31) alkanoylaminoalkyl,
32) sulfonate,
33) alkylsulfonyl,
34) alkylsulfonylaminocarbonyl,
35) arylsulfonylaminocarbonyl,
36) heterocyclylsulfonylaminocarbonyl,
37) alkenoxycarbonyl,

A3

38) alkoxycarbonylalkylaminocarbonyl,
39) aryl(carboxy)alkylaminocarbonyl,
40) carboxyalkylaminocarbonyl,
41) heterocyclylalkyl,
42) hydroxyalkylaminocarbonyl,
43) hydroxyaminocarbonyl,
44) hydroxy(carboxy)alkylaminocarbonyl,
45) hydroxy(carboxy)alkylcarbonyl, and
46) sulfoalkylaminocarbonyl,

and where Ar is an unsubstituted aryl or unsubstituted heteroaryl group, or a substituted aryl or substituted heteroaryl group, substituted by one or more than one substituent, each substituent independently selected from

A3

a. halogen,
b. alkyl,
c. aryl,
d. haloalkyl,
e. hydroxy,
f. alkoxy,
g. alkoxyalkyl,
h. alkoxycarbonyl,
i. alkoxyalkoxy,
j. hydroxyalkyl,
k. aminoalkyl,
l. aminocarbonyl,
m. alkyl(alkoxycarbonylalkyl)aminoalkyl,
n. unsubstituted heterocyclyl,
o. substituted heterocyclyl,
p. unsubstituted heterocyclylalkyl,
q. substituted heterocyclylalkyl,
r. carboxaldehyde,

s. carboxaldehyde hydrazone,

t. carboxamide,

u. alkoxycarbonylalkyl,

v. carboxy,

w. carboxyalkyl,

x. carboxyalkoxy,

y. carboxythioalkoxy,

z. carboxycycloalkoxy,

aa. alkylsulfanyl,

bb. hydroxycarbonylalkyl (carboxyalkyl),

cc. hydroxyalkylaminocarbonyl,

A3

dd. cyano,

ee. amino,

ff. heterocyclylalkylamino,

gg. carboxyalkylamino,

hh. carboxyalkenyl,

ii. alkoxycarbonylalkenyl

jj. heterocyclylalkylaminocarbonyl, and

kk. "*trans*-cinnamide",

subject to the provisos that:

i) one or more than one of R_1 or R_3 is a "*cis*-cinnamide" or a "*trans*-cinnamide", as defined above, and

ii) when R3 is a "cis-cinnamide" or a "trans-cinnamide," and R_8 is alkyl, then

(A) one or more than one of R_1, R_2, R_4, and R_5 is other than hydrogen when Ar is an unsubstituted aryl group, or

(B) Ar is a substituted aryl group, when all of R_1, R_2, R_4, and R_5 are hydrogen

Beginning on page 13, line 1 and ending on page 13, line 3:

A4

The term "alkyl" as used herein refers to a saturated straight or branched chain radical group of 1-10 carbon atoms derived from an alkane by the removal of one hydrogen. The alkyl groups of this invention can be optionally substituted with one or more than one substituent, including but not limited to, alkanoylamido, alkanoyloxy, alkoxycarbonylalkyl, alkoxy, alkoxycarbonyl, amino, aryl, arylalkyl, carboxamido, carboxy, heterocyclyl, hydroxy, hydroxyalkoxy, heterocyclyl, and sulfonate, where the aryl, and heterocyclyl groups alone, or as joined with another radical, can be optionally substituted with one or more than one substituent as described herein.

Beginning on page 13, line 17 and ending on page 13, line 19:

A5

The term "amino" as used herein refers to a radical of the form $-NR_{18}R_{19}$, or to a radical of the form NR_{18}, where R_{18} and R_{19} are independently selected from hydrogen, alkyl, alkylsulfonyl, cycloalkyl, alkanoyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxy, hydroxyalkyl, hydroxy(carboxy)alkyl, aryl, arylalkyl, arylsulfonyl, aryl(carboxy)alkyl, heterocyclyl, heterocyclylalkyl, heterocyclylamino, heterocyclylsulfonyl, carboxyalkyl, and sulfoalkyl, where the alkyl, cycloalkyl, aryl, and heterocyclyl groups alone, or as joined with another radical, can be optionally substituted with one or more than one substituent as described herein.

Beginning on page 14, line 5 and ending on page 14, line 9:

A6

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings. The aryl group can also be fused to a cyclohexane, cyclohexene, cyclopentane or cyclopentene ring. The aryl groups of this invention, unless otherwise specified, can be optionally substituted with one or more than one substituent, including but not limited to, alkyl, haloalkyl, halogen, hydroxy, carboxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxyalkoxy, hydroxyalkyl, aminoalkyl, aminocarbonyl, alkyl(alkoxycarbonylalkyl)aminoalkyl, unsubstituted heterocyclyl, substituted heterocyclyl, unsubstituted heterocyclylalkyl, substituted heterocyclylalkyl, carboxaldehyde, carboxaldehyde hydrazone, carboxamide, alkoxycarbonylalkyl, carboxyalkyl, carboxyalkoxy, carboxythioalkoxy, carboxycycloalkoxy, alkylsulfanyl,

A6

sulfonate, hydroxycarbonylalkyl (carboxyalkyl), hydroxyalkylaminocarbonyl, cyano, amino, heterocyclylalkylamino, carboxyalkylamino, carboxyalkenyl, alkoxycarbonylalkenyl, heterocyclylalkylaminocarbonyl, and "*trans*-cinnamide" substituents, where the alkyl, aryl, and heterocyclyl groups alone, or as joined with another radical, can be optionally substituted with one or more than one substituent as described herein.

Beginning on page 15, line 18 and ending on page 16, line 13:

The terms "heterocycle" or "heterocyclyl" represent a 4-, 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. The 4- and 5-membered rings have zero to two double bonds and the 6- and 7-membered rings have zero to three double bonds. The term "heterocycle" or "heterocyclic" as used herein additionally refers to bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to

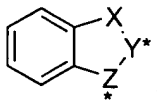
A7

one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring. Heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, oxopyrrolidinyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, triazolyl, dioxaspirodecanyl, dioxotriazaspirodecanyl, and the like.

Beginning on page 16, line 18 and ending on page 19, line 5:

Partial Enter

V unclear

Heterocyclics also include compounds of the formula  where X* and Z* are independently selected from -CH_2-, -CH_2NH-, -CH_2O-, -NH- and -O-, with the proviso that at least one of X* and Z* is not –CH_2-, and Y* is selected from -C(O)- and -$(C(R'')_2)_v$ -, where R'' is hydrogen or alkyl of one to four carbons, and v is 1-3. These heterocycles include 1,3-benzodioxolyl, 1,4-benzodioxanyl, 2,3-dihydro-1H-benzimidazol-2-one and the like. The heterocycle groups of this invention, unless otherwise specified, can be optionally substituted with one or more than one substituent, including but not limited to, alkanoyl, alkanoylamino, alkanoylaminoalkyl, alkanoyloxy, alkanoyloxyalkyl, alkenoxycarbonyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxyalkylaminocarbonyl, alkoxycarbonyl, alkoxycarbonylalkenyl, alkoxycarbonylalkyl, alkyl, alkyl(alkoxycarbonylalkyl)aminoalkyl, alkylsulfanyl, alkylsulfonyl, alkylsulfonylaminocarbonyl, amino, aminoalkanoyl, aminoalkyl, aminocarbonyl, aryl, arylalkoxycarbonyl, aryl(carboxy)alkylaminocarbonyl arylsulfonylaminocarbonyl, carboxaldehyde, carboxaldehyde hydrazone, carboxamide, carboxamidoalkyl, carboxy, carboxyalkoxy, carboxyalkenyl, carboxyalkyl, carboxyalkylamino, carboxyalkylaminocarbonyl, carboxycarbonyl, carboxycycloalkoxy, carboxythioalkoxy, cyano, cycloalkyl, haloalkyl, halogen, unsubstituted heterocyclyl, substituted heterocyclyl, unsubstituted heterocyclylalkyl, substituted heterocyclylalkylamino, heterocyclylalkylaminocarbonyl, heterocyclylcarbonyl, heterocyclylsulfonylaminocarbonyl, hydroxy, hydroxyalkanoyl, hydroxyalkoxyalkyl, hydroxyalkyl, hydroxyalkylaminocarbonyl, hydroxyaminocarbonyl, hydroxy(carboxy)alkylaminocarbonyl, hydroxy(carboxy)alkylcarbonyl, hydroxycarbonylalkyl(carboxyalkyl), sulfonate, unsubstituted tetrazolyl, substituted tetrazolyl, sulfoalkylaminocarbonyl, and "*trans*-cinnamide," substituents where the alkyl, aryl, and heterocyclyl groups alone, or as joined with another radical, can be optionally substituted with one or more than one substituent as described herein.

18

Beginning on page 18, line 18 and ending on page 19, line 2:

The term "phenyl" as used herein refers to a monocyclic carbocyclic ring system having one aromatic ring. The phenyl group can also be fused to a cyclohexane or cyclopentane ring. The phenyl groups of this invention can be optionally substituted with one or more than one substituent, including but not limited to, haloalkyl, halogen, hydroxy, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkenyl, alkoxycarbonylalkyl, alkyl, alkyl(alkoxycarbonylalkyl)aminoalkyl, amino, aminoalkyl, aminocarbonyl, carboxaldehyde, carboxaldehyde hydrazone, carboxamide, carboxy, carboxyalkenyl, carboxyalkoxy, carboxyalkyl, carboxyalkylamino, carboxycycloalkoxy, carboxythioalkoxy, cyano, unsubstituted heterocyclyl, substituted heterocyclyl, unsubstituted heterocyclylalkyl, substituted heterocyclylalkyl, heterocyclylalkylamino, heterocyclylalkylaminocarbonyl, hydroxyalkyl, hydroxyalkylaminocarbonyl, hydroxycarbonylalkyl (carboxyalkyl), sulfonate, alkylsulfanyl, or "*trans*-cinnamide" substituents. where the alkyl, aryl, and heterocyclyl groups alone, or as joined with another radical, can be optionally substituted with one or more than one substituent as described herein.

NE Unclear

Beginning on page 18, line 18 and ending on page 19, line 2:

The term "pharmaceutically-acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

NE Unclear

Beginning on page 19, line 10 and ending on page 19, line 10:

The term "sulfonate," or "sulfo" as used herein refers to the radical -SO_3H.

A9

Beginning on page 21, line 17 and ending on page 62, line 6:

Compounds of the present invention include:

(2,4-Dichlorophenyl)[2-(*E*-((6-hydroxyhexylamino)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-(*E*-((3-(1-imidazolyl)propylamino)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((2-hydroxyethylamino)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((6-hydroxyhexylamino)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((bis-(2-hydroxyethyl)amino)carbonyl)ethenyl) phenyl] sulfide;

A10

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-methylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-pyridyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2-(Hydroxymethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-hydroxyethoxyethyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((3-(hydroxymethyl)piperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((2-(hydroxymethyl)piperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((3-acetamidopyrrolidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((piperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

A10

(2-Bromophenyl)[2-chloro-4-(*E*-((4-acetylhomopiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((thiomorpholin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((2-tetrahydroisoquinolinyl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((2-(1-morpholinyl)ethylamino)carbonyl) ethenyl)phenyl] sulfide;

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((4-phenylpiperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino) carbonyl) ethenyl)phenyl] sulfide;

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((cyclopropylamino)carbonyl)ethenyl) phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl)

ethenyl)phenyl] sulfide;

(2,3-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(4-Bromophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(4-Methylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(2-furoylcarbonyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(methanesulfonyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

A10

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(diethylaminocarbonylmethyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(diethylaminocarbonyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(*tert*-butoxycarbonylmethyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carboxycarbonyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carboxymethyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

(2-Methylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Chlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Aminophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Hydroxymethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl]sulfide;

(2-Ethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-*iso*-Propylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-*tert*-Butylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Chlorophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl))2-propenyl)phenyl] sulfide;

(2-(1-Morpholinylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl) phenyl] sulfide;

(2-(4-(1,3-Benzodioxolyl-5-methyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

A10

(2-(4-(*iso*-Propylaminocarbonylmethyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2-((*N*-Ethoxycarbonylmethyl-*N*-methyl)aminomethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2-Formylphenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;

(2-(4-Formylpiperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2-(*E*-((1-Morpholinyl)carbonyl)ethenyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl) carbonyl)ethenyl)phenyl] sulfide;

(2-Formylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Formylphenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide, N,N-dimethyl hydrazone;

(2-((3-(1-Morpholinyl)propyl)-1-amino)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-bromo-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-formyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;

(2-Chloro-6-formylphenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)

phenyl] sulfide;

(2-Cyanophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-cyano-4-(*E*-((morpholin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(2-Bromophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(2-(Pyrrolidin-1-yl)phenyl)[2-chloro-4-(*E*-((morpholin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(2-Methoxyphenyl)-[2-chloro-4-(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carbomethoxypiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

A10 (2-Methylphenyl)[2-nitro-4-(*E*-((3-carboxamido-4-carbobenzoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-carbomethoxy-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-carboxy-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((morpholin -1-yl)carbonyl) ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((cyclobutylamino)carbonyl) ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((cyclopentylamino)carbonyl) ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((5-hydroxypent-1-ylamino)carbonyl) ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carbomethoxy-4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Biphenyl)[2-chloro-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3,4-Dimethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(5-Indolyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(5-Benzodioxolyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-carbomethoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10

(2,3-Dimethoxyphenyl)-[2-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Fluorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-trifluoromethyl-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-(Pyrrolidin-1-yl)phenyl)[2-trifluoromethyl-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3-Carboxamidophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(3-(Hydroxymethyl)phenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

Phenyl[2-trifluoromethyl-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((2-carbomethoxy-4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(pyridine-4-methylaminocarbonyl)-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide;

(2-Methoxyphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-(Azetidin-1-yl)phenyl)[2-trifluoromethyl-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-(Piperidin-1-yl)phenyl)[2-trifluoromethyl-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3-Chloro-2-formylphenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(2-Trifluoromethylphenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(3-Bromophenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

A10

(3,5-Dimethylphenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-dimethylaminocarbonyl-4-(pyridine-4-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-dimethylaminocarbonyl-4-carbomethoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-dimethylaminocarbonyl-4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(1-morpholinocarbonyl)-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(pyridine-4-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-dimethylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(benzylaminocarbonyl)-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(dimethylaminocarbonyl)-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(E-((3-(5*S*-hydroxymethyl-2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-chloro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-chloro-4-(E-(N-methyl-N-(3-(2-oxyopyrrolidin-1-yl)prop-1-yl)amino)carbonyl) ethenyl)phenyl]sulfide;

(2-[2-Methoxy]ethoxyphenyl)-[2-chloro-4-(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(morpholinocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10 (2-Isopropylphenyl)[2-nitro-4-(*E*-((4-methoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-(4-(pyridine-4-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(pyridine-3-methylaminocarbonyl)-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(pyridine-2-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(pyridine-3-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(4-Hydroxyphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-l)carbonyl)ethenyl)phenyl]sulfide;

(3,5-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-chloro-4-(E-((3-(5*S*-acetoxymethyl-2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-chloro-4-(E-((3-(5*S*-methoxymethyl-2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-chloro-4-(E-((3-(4*R*-hydroxy-2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

Phenyl[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;
(2-Dimethylaminophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide;
(3-((2-Hydroxyethyl)aminocarbonyl)phenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
(3-((3-(1-Imidazolyl)propyl)aminocarbonyl)phenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
(3-((2-(1-Morpholinyl)ethyl)aminocarbonyl)phenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-hydroxymethyl-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
A10 (2-Isopropylphenyl)[2-nitro-4-(*E*-((4-formylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-hydroxymethyl-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
(2-Ethoxyphenyl)-[2-chloro-4(E-[(3-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl) phenyl]sulfide;
(3- Aminophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;
(4-Aminophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;
(2,4-Dimethylphenyl)[2- nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;
(2,5-Dimethylphenyl)[2- nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;
(4-Methoxyphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;
(3-Chlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;
(2-Chloro-4,5-diaminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
(3,4-Diaminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl]sulfide;

(6-Chloro-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-7-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Hydroxy-4-aminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-(pyridine-2-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-(pyridine-3-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-carbomethoxy-4-methoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-carboxy-4-methoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carbomethoxy-4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(2-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl) phenyl]sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-3-ylamino)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)-[2-chloro-4(*E*-[(2-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-(((pyrrolidin-3-ene-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((4-(ethoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((4-(2-furylcarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(3-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl) phenyl]sulfide;

(2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-ethoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-isopropoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-isobutoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-((1-propen-2-oxy)carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-propionylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-carboxamidopiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-methylaminocarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-hydroxyacetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-(pyrazine-2-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-(((2-carboxypyrrol-3-ene-1-yl)carbonyl)ethenyl) phenyl] sulfide methyl ester;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-hydroxymethyl-4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-(((2-carboxypyrrol-3-ene-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-(((2-hydroxymethylpyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-cyclopropylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboxamidopiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carbomethoxy-4-oxopiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3,5-dimethylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Ethylindol-7-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3-[2-Methoxy]ethoxyphenyl)-[2-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(E-((4,4'-*S*-dioxythiomorpholin-1-yl)carbonyl) ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-chloro-4-(E-(N-carbomethoxymethyl-N-(3-(2-oxopyrrolidin-1-yl)prop-1-yl)amino)carbonyl) ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-chloro-4-(E-((4-*S*-oxythiomorpholin-1-yl)carbonyl) ethenyl)phenyl]sulfide;

(2-Methoxy-5-chlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-acetoxymethyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3,5-dimethyl-4-acetyl-piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

A10

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*Z*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((6-methylpyrid-2-ylamino)carbonyl)ethenyl) phenyl] sulfide;

(2-Methyl-3-chlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((3-carboxamidopiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((2-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((4-carboxamidopiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((4-*tert*-butoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((*syn*-3,5-dimethylmorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((*anti*-3,5-dimethylmorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboethoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-isopropoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(dimethylaminocarbonyl)-4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carbomethoxy-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10 (2-Isopropylphenyl)[2-nitro-4-(*E*-((3-hydroxymethyl-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((2-carbomethoxy-4-(methoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((2-carbomethoxy-4-methyl piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((2-carboxy-4-(methoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Indol-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Ethyl-3-(dimethylaminomethyl)indol-7-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(5-Ethoxybenzodioxan-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethyl-4-bromophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((2-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((4-carboxymethylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(3-Morpholinophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(5-Ethoxybenzodioxan-8-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(5-Chloro-8-ethoxyquinolin-7-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-ethanesulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10 (2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-(4-methylpiperazine) sulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-*p*-toluenesulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-methyl-4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Hydroxyphenyl)-[2-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide;

(1-(Carboxymethyl)indol-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino) carbonyl)ethenyl) phenyl] sulfide;

(3-(2-Morpholinoethylamino)phenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Pyrrolidin-1-ylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3-Bromophenyl)[2-nitro-4-(*E*-((3-carboethoxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3-Bromophenyl)[2-nitro-4-(*E*-((4-carboethoxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-(Hydroxymethyl)-benzodioxan-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(3-(Dimethylaminomethyl)indol-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10 (2-Isopropylphenyl)[2-nitro-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((4-*p*-toluenesulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboxy-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carboxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-carbomethoxy-4-*tert*-butoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-carbomethoxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-carbomethoxypiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Methyl-3-(carboethoxymethyl)indol-5-yl)[2-trifluoromethyl-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-(2-Methoxyethyl)indol-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10 (2-Isopropylphenyl)[2-nitro-4-(*E*-((3-acetoxymethyl-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(dimethylaminocarbonyl)-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-cyanomorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboethoxymorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(tetrazol-5-yl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-carbomethoxypiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-aza-6,9-dioxaspiro[5.4]decan-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoro-4-(*E*-((4-(2-oxo-2,3-dihydro-1H-benzimidazole-1-yl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-(methylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carbomethoxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboxymorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-carboxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-aza-6,9-dioxaspiro[5.4]decan-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-(dimethylaminomethyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((piperidin-1-ylamino)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carboxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-(Dimethylaminocarbonyl)-benzodioxan-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(2-(methoxymethyl)tetrazol-5-yl) piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(1-(methoxymethyl)tetrazol-5-yl) piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino) carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(tetrazol-5-yl) piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-(1-methylpyrrolidin-2-yl)ethylamino)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-sulfopiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-((ethanesulfonylamino)carbonyl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-((*p*-toluenesulfonylamino)carbonyl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-((ethanesulfonylamino)carbonyl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-(tetrazol-5-yl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-butyl-5-(tetrazol-5-yl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(3-Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl]sulfide;

(2-(and 3-)(Aminomethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(methylaminocarbonyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(hydroxymethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(acetoxymethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(aminomethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(acetamidomethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((2-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Methoxyphenyl)-[2,3-dichloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)-[2,3-dimethyl-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((indol-5-ylamino)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((3-(tetrazol-5-yl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((2-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((3-(tetrazol-5-yl)morpholin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((4-(methylaminocarbonyl)piperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Methoxyphenyl)-[2,3-dichloro-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide;

A10 (Benzodioxan-6-yl)[2-chloro-4-(*E*-((4-(tetrazol-5-yl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Methoxyphenyl)-[3-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-oxopiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-*R*-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-*R*-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2,3-dichloro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((4-acetylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino) carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((4-acetylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

A10

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)-[2,3-dichloro-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)-[2,3-dichloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Ethoxyphenyl)-[2,3-dichloro-4-(*E*-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboethoxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2,3-difluoro-4-(*E*-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2,3-difluoro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2,3-difluoro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-ethoxycarbonylpyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carboxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

A10

(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl) [4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl)naphthyl] sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-2,4-dioxo-1,3,8-triazaspiro[4.5])-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2,3-dichloro-4-(*E*-((4-ethylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(Benzodioxan-6-yl)[2,3-bis(trifluoromethyl)-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(E-((4-(carboxymethylamino)carbonyl-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-carboxymethylpiperazin-1-yl) carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-N-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-((4-(carbo-2,3-dihydroxypropylamino)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-(4-(2,3-dihydroxypropionyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-(4-(2,3-dihydroxy-3-carboxypropionyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-((4-(carboxymethylamino)carbonyl-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

A10 (1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-((4-sulfopiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(4-methylhomopiperazin-1-ylcarbonyl)ethenyl)phenyl] sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(4-tetrahydrofuroylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(Benzodioxan-6-yl)[2-(benzodioxan-6-sulfanyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-amino-4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2,3-dichloro-4-((4-furoylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(4-(carbo-3-sulfopropylamino)piperadin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2,3-dichloro-4-(*E*-(4-acetylamino-4-carboxypiperidin-1-ylcarbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) 5-[8-(E-((4-(aminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)quinolinyl]sulfide;

(2-Methoxyphenyl) [2-trifluoromethyl-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(1-Methylindol-5-yl)[2,3-dichloro-4-(E-(((1S,4S)-5-tert-butyloxycarbonyl-2,5-diazabicyclo(2.2.1)heptan-2-yl)carbonyl)ethenyl)phenyl]sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E/Z*-((1S,4S)-2,5-diazabicyclo(2.2.1)heptan-2-ylcarbonyl)ethenyl)phenyl] sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(4-hydroxy-3-carboxypiperidin-1-ylcarbonyl)ethenyl)phenyl] sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(S-oxothiomorpholin-1-ylcarbonyl)ethenyl)phenyl] sulfide;

A10

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-sulfophenylamino)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-carboxyphenylamino)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Morpholino)phenyl] [2,3-dichloro-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-phenylcarboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-(((4-hydroxylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((N-carboxymethyl-N-phenylamino)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [3-chloro-6-hydroxy-4-(E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-(4-((1-(2-phenyl-1-carboxyethyl)amino)carbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-(4-((1-(2-hydroxy-1-carboxyethyl)amino)carbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(3-(1-(3-Carboxypiperidinyl)phenyl)[2,3-dichloro-4-(E-((1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(3-(4-Pyrrolidin-1-yl)piperidin-1-yl)phenyl) [2,3-dichloro-4-(E-(((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl)ethenyl)phenyl]sulfide;

A10 [3-(4-(Spiro-2,2-dioxolanyl)piperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl]sulfide;

[3-(3-Carboxylpiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-(2-Carboxy)ethenyl)phenyl) [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Carboxylpiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-[(1,2,3,6-tetrahydropyridin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

[3-(4-Carboxylpiperidinyl)phenyl] [2,3-dichloro-4-(*E*-[(4-morpholinyl)carbonyl]ethenyl)phenyl] sulfide;

[2-(4-Acetylpiperazin-1-yl)phenyl] [2,3-dichloro-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

3-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-[(4-morpholinyl)carbonyl]ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-[(4-(dimethylaminosulfamoyl)piperazin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2,3-bis(trifluoromethyl)-4-(E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((2-carboxypyrrolidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-((trifluoromethylsulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2,3-dichloro-4-(*E*-(piperidin-1-ylcarbonyl)ethenyl)phenyl] sulfide;

(2-Hydroxyphenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(E-((((4-carboxyphenyl)methyl)amino)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(E-(((4-pyrrolidin-1-yl)piperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

A10

(2-Hydroxyphenyl)[2,3-dichloro-4-(E-((4- carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-((methylsulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Aminophenyl) [2,3-dichloro-4-(*E*-((4-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;

(3-(4-carboxypiperidin-1-yl)phenyl)[2,3-dichloro-4-(*E*-((S-oxothiomorpholin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Glycoxyphenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

(2-(4-Butyroxy)phenyl)[2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-hydroxyethylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-furoylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((pyrrolidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((diethylaminocarbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-ethylpiperazin-yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-(aminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-(2-(ethoxyethyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[3-((4-Carboxymethyl)piperazin-1-yl)phenyl] [(2,3-dichloro-4-(E-(4-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

A10

(3-Hydroxyphenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Butyroxy)phenyl] [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

(2-Hydroxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

(3-Hydroxyphenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl-4-(*E*-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl-4-(*E*-((1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[2-((4-Carboxy)butyloxy)phenyl] [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

(2-Glycoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

(2-(4-Butyroxy)phenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-((bis-(2-ethoxyethyl)amino)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis-(trifluoromethyl)-4-(*E*-((bis-(2-hydroxypropyl)amino)carbonyl)ethenyl)phenyl] sulfide;
[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis-(trifluoromethyl)-4-(*E*-((piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
(3-(4-Butyroxy)phenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;
[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-[(3-(2-oxopyrrolidin-1-yl)propylaminocarbonyl)ethenyl)phenyl] sulfide;
A10 [2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-[(3-(2-oxopyrrolidin-1-yl)propylaminocarbonyl)ethenyl)phenyl] sulfide;
[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-((1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-((4-(2-(hydroxyethoxy)ethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide; and
(3-(3-Propioxy)phenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide.

Beginning on page 64, line 1 and ending on page 64, line 8:

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of
A11 microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

Beginning on page 65, line 5 and ending on page 65, line 18:

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically-acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

A12

Beginning on page 68, line 1 and ending on page 69, line 17:

The compounds of the present invention may be used in the form of pharmaceutically-acceptable salts derived from inorganic or organic acids. By "pharmaceutically-acceptable salt" is meant those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically-acceptable salts are

A13

well-known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically-acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: 1 et seq. The salts may be prepared *in situ* during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate (isethionate), A13 lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water-soluble, or oil-soluble or dispersible products are thereby obtained. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a

pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically-acceptable basic addition salts include cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

A13

Beginning on page 75, line 6 and ending on page 75, line 20:

A further method for producing diarylsulfide cinnamides is shown in Scheme 7, wherein the diaryl sulfide is formed through coupling of a suitably protected aryl thiol **28** to an activated cinnamate ester **27**. Substituted phenol **24** may be brominated to give bromophenol **25**. Heck-type coupling of bromide **25** with an appropriate olefinic substrate, for example methyl acrylate, is effected with palladium catalysis, leading to the cinnamate ester **26**. The phenol is then activated towards further reaction, for example by conversion to the corresponding triflate **27** under standard conditions. The required protected thiol **28** may be prepared by the method of Soderquist, et al. (*Tetrahedron Lett.* **1994**, *35*, 3221-3224), by coupling an aryl halide or triflate with triisopropylsilyl thiol under palladium catalysis. The two partners **27** and **28** are then reacted in the presence of a fluoride source, for example cesium fluoride, to provide the diarylsulfide cinnamate **29**. Hydrolysis is accomplished by basic media, such as lithium or sodium hydroxide in

A14

A14

water-THF, and the resulting acid **30** is coupled to amines under standard amide-bond forming conditions (for example, EDC/HOBt) to produce the amides **31**.

Beginning on page 76, line 11 and ending on page 77, line 8:

Compounds which contain trifluoromethyl groups on the cinnamide-portion of the compounds were made by the method shown in Scheme 9. According to the method of Chambers (Chambers,R.D.; Roche,, A.; and Rock,M.H. (*J. Chem. Soc., Perkin Trans. 1* **1996**, 1095) (Ref), Diels-Alder reaction between 1,1,1,4,4,4-hexafluoro-2-butyne and 2-methylfuran led to bicyclic ether **35**, which was rearranged with Lewis acid (for example, boron trifluoride etherate) to the phenol **36**. The methyl group is then converted to the corresponding aldehyde **37** by bromination followed by reaction with dimethylsulfoxide. Using the analogous procedures described for Scheme 1 above, the phenol was activated and condensed with thiols under basic conditions to afford diarylsulfide aldehydes **38**, and further converted to cinnamides **39** by the previously described procedures.

A15

Beginning on page 77, line 11 and ending on page 77, line 16:

Cinnamides bearing more complex substituted piperidine amides can be produced by the methods outlined in Scheme 10 and 11. Cinnamic acids **40** are coupled to spirohydantoin piperidine **41**, and the derived amide **42** is first reacted with an activating reagent (for example di-tert-butyl dicarbonate), and then hydrolyzed to the amino acid **43**. The derived amino group may then be reacted further, for example with acid anhydrides or acid chlorides, to produce amides **44**.

A16

Beginning on page 80, line 4 and ending on page 80, line 17:

A process for preparing analogs with amino substitutions of the aryl portion of the sulfides is illustrated in Scheme 14. The intermediate triflate **27** is reacted with halo-substituted thiophenols **54** (X = Br, Cl, OTf, OTs) under basic catalysis, to provide the sulfide derivative **55**. The halogen or activated hydroxyl is then substituted with an amine, using the method of Buchwald (Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722-9723). Similar transition-metal catalyzed reactions may be applied, see, for example, the method of Hartwig (Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369-7370). The NR_3R_4 group may constitute a cyclic or acyclic group, optionally substituted with additional functionalities that may enhance the activities of the compounds, and further synthetic transformations familiar to those skilled in the art may be applied. For instance, ester groups may be hydrolyzed to the corresponding carboxylic acids or amides. The derived anilino sulfides may then be processed as described above to produce the cinnamides **57**.

A17

Beginning on page 93, line 20 and ending on page 111, line 11:

Example 3

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((2-hydroxyethylamino)carbonyl) ethenyl)phenyl] sulfide

A18

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with ethanolamine. Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.57 (q, J = 7.65 Hz, 2H), 3.71 (q, J = 7.65 Hz, 2H), 6.06 (br s, 1H), 6.40 (d, J = 15.3 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 7.22-7.30 (m, 4H), 7.49-7.60 (m, 1H), 7.55 (d, J = 15.3 Hz,1H). MS (APCI)

$(M+H)^+$ at *m/z* 402, 404, 406, 408. Analysis calculated for $C_{17}H_{14}N_1O_2Cl_3S_1$ $0.25H_2O$: C, 50.14; H, 3.59; N, 3.44. Found: C, 50.16; H, 3.62; N, 3.29.

Example 4

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((6-hydroxyhexylamino)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde. Colorless oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (m, 4H), 1.58 (m, 4H), 3.40 (q, J = 6.7 Hz, 2H), 3.65 (br m, 2H), 5.60 (br t, 1H), 6.35 (d, J = 15.3 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.22-7.30 (m, 4H), 7.49-7.60 (m, 1H), 7.55 (d, J = 15.3 Hz, 1H). MS (APCI) $(M+H)^+$ at *m/z* 458, 460, 462, 464. Analysis calculated for $C_{21}H_{22}N_1O_2Cl_3S_1$ $0.27H_2O$: C, 54.39; H, 4.90; N, 3.02. Found: C, 54.40; H, 4.85; N, 2.71.

Example 5

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((*bis*-(2-hydroxyethyl)amino)carbonyl) ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro- benzaldehyde, and 6-amino-1-hexanol with diethanolamine. Colorless oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.99 (br s, 2H), 3.67 (br m, 4H), 3.88 (t, J = 5.1 Hz, 2H), 3.94 (t, J = 5.1 Hz, 2H), 6.94 (d, J = 15.3 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.21-7.32 (m, 3H), 7.50-7.54 (m, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.58 (d, J = 15.3 Hz, 1H). MS (APCI) $(M+H)^+$ at *m/z* 446, 448, 450, 452.

Analysis calculated for $C_{19}H_{18}N_1O_3Cl_3S_1$ $1.09H_2O$: C, 48.93; H, 4.36; N, 3.00. Found: C, 48.88; H, 4.00; N, 3.01.

Example 6

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl) ethenyl)phenyl] sulfide

A18

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-(3-aminopropyl)-2-pyrrolidinone. Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74 (qu, J = 6.0 Hz, 2H), 2.09 (qu, J = 7.5 Hz, 2H), 2.45 (t, J = 8.25 Hz, 2H), 3.33 (q, J = 6.0 Hz, 2H), 3.42 (q, J = 8.25 Hz, 4H), 6.46 (d, J = 15.6 Hz, 1H), 7.02 (d, J = 8.7 Hz, 1H), 7.14-7.23 (m, 2H), 7.30 (dd, J = 2.4, 8.7 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 15.6 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 483, 485, 487, 489. Analysis calculated for $C_{22}H_{21}N_2O_2Cl_3S_1$ $0.57H_2O$: C, 53.48; H, 4.52; N, 5.67. Found: C, 53.49; H, 4.60; N, 5.65.

Example 7

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with morpholine. White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.59-3.80 (m, 8H), 6.83 (d, J = 15.6 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.16-7.32 (m, 3H), 7.49-7.53 (m, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 15.6 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z*

428, 430, 432, 434. Analysis calculated for $C_{19}H_{16}N_1O_2Cl_3S_1$ $0.46H_2O$: C, 52.22; H, 3.90; N, 3.20. Found: C, 52.20; H, 3.76; N, 3.12.

Example 8

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-methylpiperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-methylpiperazine. Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 2.51 (br m, 4H), 3.63-3.87 (br m, 4H), 6.85 (d, J = 15.6 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.19-7.25 (m, 2H), 7.27 (dd, J = 2.1, 8.7 Hz, 1H), 7.52 (t, J = 0.9 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 441, 443, 445, 447. Analysis calculated for $C_{20}H_{19}N_2O_1Cl_3S_1$ $0.45H_2O$: C, 53.39; H, 4.46; N, 6.23. Found: C, 53.37; H, 4.46; N, 6.07.

A18

Example 9

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-acetylpiperazine. White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), 3.50-3.58 (m, 2H), 3.58-3.85 (m, 6H), 6.85 (d, J = 15.3 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 7.24-7.36 (m, 3H), 7.54 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 15.3 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 486, 488, 490, 492. Analysis calculated for $C_{21}H_{19}N_2O_2Cl_3S_1$ $0.85H_2O$: C, 51.99; H, 4.30; N, 5.77. Found: C, 52.03; H, 4.27; N, 5.67.

Example 10

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-pyridyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro- benzaldehyde, and 6-amino-1-hexanol with 1-(2-pyridyl)piperazine. White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.59 (br m, 2H), 3.69 (br m, 2H), 3.78 (br m, 2H), 3.86 (br m, 2H), 6.64-6.72 (m, 2H), 6.90 (d, J = 15.6 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 7.22-7.25 (m, 2H), 7.31(dd, J = 2.4, 8.7 Hz, 1H), 7.49-7.57 (m, 2H), 7.61 (d, J = 15.6 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 8.19-8.24 (m, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 504, 506, 508, 510. Analysis calculated for $C_{24}H_{20}N_3O_1Cl_3S_1$: C, 57.10; H, 3.99; N, 8.32. Found: C, 57.12; H, 4.06; N, 8.29.

A18

Example 11

(2-(Hydroxymethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-mercaptobenzyl alcohol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with morpholine. White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.50-3.62 (br m, 6H), 3.65-3.74 (br m, 2H), 4.54 (d, J = 5.7 Hz, 2H), 5.33 (t, J = 5.7 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 15.0 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 15.0 Hz, 1H), 7.43 (dd, J = 1.8, 8.7 Hz, 1H), 7.50 (dd, J = 2.1, 8.7 Hz, 1H), 7.55 (dd, J = 2.1, 7.8 Hz, 1H), 7.68 (dd, J = 1.5, 8.1 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 390, 392. Analysis calculated for $C_{20}H_{20}N_1O_3Cl_1S_1 \cdot 0.09H_2O$: C, 61.35; H, 5.20; N, 3.58. Found: C, 61.37; H, 5.48; N, 3.81.

Example 12

(2-Bromophenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with morpholine. White solid; ^{1}H NMR (d^6-DMSO, 300 MHz) δ 3.50-3.66 (br m, 6H), 3.66-3.79 (br m, 2H), 7.05 (d, *J* = 8.7 Hz, 1H), 7.26 (dd, *J* = 2.1, 8.1 Hz, 1H), 7.33 (dd, *J* = 2.1, 8.1 Hz, 1H), 7.36 (d, *J* = 15.6 Hz, 1H), 7.39 (dd, *J* = 1.8, 12.0 Hz, 1H), 7.45 (dd, *J* = 1.8, 6.3 Hz, 1H), 7.48 (d, *J* = 15.6 Hz,1H), 7.64 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.80 (dd, *J* = 2.8, 8.7 Hz, 1H), 8.09 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 438, 440, 442.

A 18

Example 13

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzadehyde, and 6-amino-1-hexanol with 1-hydroxyethylpiperazine. Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.85-3.20 (br m, 6H), 3.84-4.19 (m, 6H), 6.80 (d, *J* = 15.3 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 7.22-7.38 (m, 3H), 7.50-7.56 (m, 1H), 7.56-7.62 (m, 1H), 7.60 (d, *J* = 15.3 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 471, 473, 475, 477.

Example 14

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-hydroxyethoxyethyl)piperazin-1-yl) carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-

hexanol with 1-[2-(2-hydroxyethoxy)ethyl]piperazine. Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.73 (br m, 6H), 3.58-3.68 (m, 2H), 3.68-4.00 (m, 8H), 6.84 (d, J = 15.3 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.20-7.34 (m, 3H), 7.54 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 15.3 Hz, 1H), 7.58-7.65 (overlapping d, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 515, 517, 519, 521.

Example 15

(2-Bromophenyl)[2-chloro-4-(*E*-((3-(hydroxymethyl)piperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 3-hydroxymethylpiperidine. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.07 (d, J = 17.7 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.63 (br d, J = 7.7 Hz, 1H), 7.44 (d, J = 7.0 Hz, 1H), 7.40 (br s, 2H), 7.35 (m, 1H), 7.25 (dd 7.7, 1.5, 1H), 7.06 (dd, J = 8.1, 2.9, 1H), 4.57 (m, 1H), 4.45 (m, 1H), 4.16 (br m, 2H), 1.2 – 1.8 (m, 8H). HRMS calculated for $C_{21}H_{21}N_1O_2S_1Br_1Cl_1$: 466.0243. Observed: 466.0247.

Example 16

(2-Bromophenyl)[2-chloro-4-(*E*-((2-(hydroxymethyl)piperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 2-hydroxymethylpiperidine. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.03 (m, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.61 (m, 1H), 7.30 – 7.45 (m, 4H), 7.23 (m, 1H), 7.07 (m, 1H), 4.79 (m,

2H), 4.61 (m, 2H), 4.10 (m, 1H), 1.50 (m, 6H). HRMS calculated for $C_{21}H_{21}N_1O_2S_1Br_1Cl_1$: 466.0243. Observed: 466.0247.

Example 17

(2-Bromophenyl)[2-chloro-4-(*E*-((3-acetamidopyrrolidin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 3-acetamidopyrrolidine. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.14 (m, 1H), 8.07 (dd, J = 9.8, 1.7 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.64 (dd, J = 8.1, 1.7 Hz, 1H), 7.25 – 7.47 (m, 4H), 7.10 (t, J = 7.8 Hz, 1H), 7.03 (dd, J = 8.1, 1.7 Hz, 1H), 3.45 – 4.34 (m, 6H), 2.02 (m, 2H), 1.81 (ap d, J = 1.4 Hz, 1H). HRMS calculated for $C_{21}H_{20}N_2O_2S_1Br_1Cl_1$: 479.0196. Observed: 479.0183.

Example 18

(2-Bromophenyl)[2-chloro-4-(*E*-((4-hydroxypiperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 4-hydroxypiperidine. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.08 (d, J = 1.7 Hz, 1H), 7.80 (dd, J = 8.0, 1.5 Hz, 1H), 7.63 (dd, J = 8.3, 1.9 Hz, 1H), 7.44 (ap dd, J = 7.5, 1.4 Hz, 2H), 7.40 (ap d, J = 3.7 Hz, 2H), 7.34 (dt, J = 7.6, 1.8 Hz, 1H), 7.25 (dd, J = 7.5,1.7 Hz 1H), 7.05 (d, J = 8.1 Hz, 1H),

4.76 (br s, 1H), 4.01 (m, 2H), 3.72 (m, 1H), 3.12 (m, 1H), 1.75 (m, 2H), 1.32 (m, 2H). HRMS calculated for $C_{20}H_{19}N_1O_2S_1Br_1Cl_1$: 452.0087. Observed: 452.0076.

Example 19

(2-Bromophenyl)[2-chloro-4-(*E*-((piperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with piperidine. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.08 (d, J = 1.7 Hz, 1H), 7.80 (dd, J = 8.1, 1.4 Hz, 1H), 7.63 (dd, J = 8.1, 1.7 Hz, 1H), 7.44 (ap dd, J = 7.6, 1.5 Hz, 1H), 7.39 (ap d, J = 4.8 Hz, 2H), 7.34 (dt, J = 7.5, 1.6, 1H), 7.24 (dd, J = 7.5, 1.7, 1H), 7.05 (d, J = 8.1 Hz, 1H), 3.65 (br m, 2H), 3.53 (br m, 2H), 1.62 (br m, 2H), 1.50 (br m, 4H). HRMS calculated for $C_{20}H_{19}N_1O_1S_1Br_1Cl_1$: 436.0130. Observed: 436.0122.

A18

Example 20

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with nipecotic acid. Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44-1.68 (br m, 1H), 1.68-2.00 (br m, 2H), 2.51-2.67 (br m, 1H), 3.13-3.37 (br m, 1H), 3.80-4.12 (br m, 1H), 4.30-5.00 (br m, 3H), 6.86 (d, J = 15.3 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 7.16-7.24 (m, 2H), 7.29 (d, J = 8.7 Hz, 1H), 7.47-7.55 (m, 1H), 7.55 (d, J = 15.3 Hz, 1H), 7.60 (br d, 1H). MS (APCI) $(M+H)^+$ at *m/z* 470, 472, 474, 476.

Example 21

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with isonipecotic acid. Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68-1.85 (m, 2H), 1.98-2.09 (m, 2H), 2.60-2.72 (m, 1H), 2.90-3.13 (br m, 1H), 3.17-3.38 (br m, 1H), 3.93-4.12 (br m, 1H), 4.38-4.59 (br m, 1H), 6.86 (d, J = 15.3 Hz, 1H), 6.99 (dd, J = 8.7 Hz, 1H), 7.20-7.25 (m, 2H), 7.28 (dd, J = 1.8, 8.7 Hz, 1H), 7.49-7.53 (m, 1H), 7.56 (d, J = 15.3 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H). MS (APCI) $(M+H)^+$ at *m/z* 470, 472, 474, 476.

Example 22

(2-Bromophenyl)[2-chloro-4-(*E*-((4-acetylhomopiperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 4-acetylhomopiperazine. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.10 (m, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.64 (m, 1H), 7.24 – 7.51 (m, 5H), 7.05 (m, 1H), 3.39 – 3.77 (m, 8H), 1.97 (m, 3H), 1.68 (m, 2H). HRMS calculated for $C_{22}H_{22}N_2O_2S_1Br_1Cl_1$: 493.0352. Observed: 493.0352.

Example 23

(2-Bromophenyl)[2-chloro-4-(*E*-((thiomorpholin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with thiomorpholine. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.10 (d, J = 1.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.64 (dd, J = 8.1, 1.5 Hz, 1H), 7.31 – 7.48 (m, 4H), 7.36 (m, 1H), 7.26 (dd, J = 8.1, 1.8 Hz, 1H), 7.05 (d J = 8.1 Hz, 1H), 3.96 (m, 2H), 3.82 (m, 2H), 2.62 (m, 4H). HRMS calculated for $C_{19}H_{17}N_1O_1S_2Br_1Cl_1$: 455.9681. Observed: 455.9676.

A 18

Example 24

(2-Bromophenyl)[2-chloro-4-(*E*-((4-([2-oxo-2,3,dihydro-1H-benzimidazol-1-yl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.14 (d, J = 1.5 Hz, 1H), 7.80 (dd, J = 7.9, 1.3 Hz, 1H), 7.67 (dd, J = 8.1, 1.8 Hz, 1H), 7.48 (ap s, 2H), 7.44 (dt, J = 7.5, 1.2, 1H), 7.34 (dt, J = 7.6, 1.6, 1H), 7.26 (dd, J = 7.7, 1.8 Hz, 1H), 7.22 (m, 1H), 7.06 (d, J = 8.1, 1H), 6.97 (ap d, J = 2.6, 3H), 4.64 (m, 1H), 4.48 (m, 2H), 2.79 (m, 2H), 2.29 (m, 2H), 1.78 (m, 2H). HRMS calculated for $C_{27}H_{23}N_3O_2S_1Br_1Cl_1$: 568.0461. Observed: 568.0477.

Example 25

(2-Bromophenyl)[2-chloro-4-(*E*-((2-tetrahydroisoquinolinyl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with tetrahydroisoquinoline. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.12 (d, J = 7.4 Hz, 1H), 7.81 (dd, J = 7.7, 1.1 Hz, 1H), 7.67 (dd, J = 8.3, 1.3 Hz, 1H), 7.47 (m, 2H), 7.43 (dd, J = 7.5, 1.3 Hz, 2H), 7.34 (dt, J = 7.6, 1.7 Hz, 1H), 7.27 (d 7.7 Hz, 1H), 7.19 (m, 4H), 7.05 (d, J = 8.1 Hz, 1H), 4.92 (s, 1H), 4.72 (s, 1H), 3.95 (t, J = 5.9 Hz, 1H), 3.78 (t, J = 5.7 Hz, 1H), 2.89 (t, J=5.3 Hz, 1H), 2.83 (t, J=3.7, 1H). HRMS calculated for $C_{24}H_{19}N_1O_2S_1Br_1Cl_1$: 484.0138. Observed: 484.0128.

A18

Example 26

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethyl benzaldehyde, and 6-amino-1-hexanol with 1-acetylpiperazine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.79 (s, 1H); 7.63 (d, J = 15.4Hz, 1H); 7.51 (d, J = 6.8 Hz, 1H); 7.41-7.33 (m, 3H); 7.28 (m, 1H); 6.83 (d, J = 15.4 Hz, 1H); 6.79 (d, J = 6.8 Hz, 1H); 3.80-3.60 (m, 6H); 3.57-3.50 (m, 2H); 2.34 (s, 3H); 2.14 (s, 3H). MS (ESI) *m/z* 919 $(2M+Na)^+$, 897 $(2M+H)^+$, 471 $(M+Na)^+$, 449 $(M+H)^+$.

Example 27

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethyl benzaldehyde, and 6-amino-1-hexanol with morpholine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.79 (s, 1H); 7.63 (d, J = 14.0 Hz, 1H); 7.52 (d, J = 7.6 Hz, 1H); 7.40-7.30 (m, 3H); 7.28 (m, 1H); 6.87 (d, J = 14.0 Hz, 1H); 6.84 (d, J = 7.6 Hz, 1H); 3.73 (br s, 8H); 2.34 (s, 3H). MS (ESI) *m/z* 837 $(2M+Na)^+$, 815 $(2M+H)^+$, 408 $(M+H)^+$.

Example 28

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((2-(1-morpholinyl)ethylamino)carbonyl) ethenyl)phenyl] sulfide

A18

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethyl benzaldehyde, and 6-amino-1-hexanol with 2-(1-morpholinyl)ethylamine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.80 (s, 1H); 7.56 (d, J = 15.8 Hz, 1H); 7.50 (d, J = 8.1 Hz, 1H); 7.40-7.32 (m, 3H); 7.28 (m, 1H); 6.79 (d, J = 15.8 Hz, 1H); 6.40 (d, J = 8.1 Hz, 1H); 3.75 (t, J = 4.6 Hz, 4H); 3.51 (q, J = 5.5 Hz, 2H), 2.57 (t, J = 5.8 Hz, 2H); 2.55-2.48 (m, 4H); 2.34 (s, 3H). MS (ESI) *m/z* 923 $(2M+Na)^+$, 473 $(M+Na)^+$, 451 $(M+H)^+$.

Example 29

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((4-phenylpiperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde

with 4-fluoro-3-trifluoromethyl benzaldehyde, and 6-amino-1-hexanol with 4-phenylpiperazine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.81 (s, 1H); 7.64 (d, J = 16.0 Hz, 1H); 7.51 (d, J = 8.2 Hz, 1H); 7.40-7.27 (m, 6H); 6.98-6.90 (m, 4H); 6.80 (d, J = 8.2 Hz, 1H); 3.88 (br s, 4H); 2.23 (br s, 4H); 2.34 (s, 3H). MS (ESI) *m/z* 987 $(2M+Na)^+$, 965 $(2M+H)^+$, 505 $(M+Na)^+$, 483 $(M+H)^+$, 451.

Example 30

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethyl benzaldehyde, and 6-amino-1-hexanol with 3-(2-oxopyrrolidin-1-yl)propylamine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.78 (s, 1H); 7.53 (d, J = 15.6 Hz, 1H); 7.49 (d, J = 7.2 Hz, 1H); 7.40-7.33 (m, 3H); 7.14 (m, 1H); 6.80 (d, J = 8.2 Hz, 1H); 6.43 (d, J = 15.6 Hz, 1H); 3.41 (m, 4H); 3.32 (q, J = 6.1 Hz, 2H); 2.43 (t, J = 6.6 Hz, 2H); 2.34 (s, 3H), 2.08 (m, 2H), 1.75 (m, 2H). MS (ESI) *m/z* 947 $(2M+Na)^+$, 925 $(2M+H)^+$, 485 $(M+Na)^+$, 463 $(M+H)^+$.

A18

Example 31

(2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((cyclopropylamino)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethyl benzaldehyde, and 6-amino-1-hexanol with cyclopropylamine.

^{1}H NMR ($CDCl_3$, 300MHz) δ 7.76 (s, 1H); 7.56 (d, J = 15.4 Hz, 1H); 7.50 (d, J = 8.4 Hz, 1H); 7.40-7.30 (m, 3H); 7.28 (m, 1H); 6.88 (d, J = 8.4 Hz, 1H); 6.30 (d, J = 15.4 Hz, 1H); 5.70 (br s, 1H), 2.95 (m, 1H); 2.34 (s, 3H); 0.85 (m, 2H); 0.57 (m, 2H). MS (ESI) *m/z* 777 $(2M+Na)^+$, 755 $(2M+H)^+$, 400 $(M+Na)^+$, 378 $(M+H)^+$.

Example 32

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

A19

Example 32A

1-Chloro-2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) benzene

To a stirred solution of *trans*-4-chloro-3-nitrocinnamic acid (1.50 g, 6.59 mmol) and 1-acetylpiperazine (0.89 g, 6.94 mmol) in 20 mL of DMF at room temperature was added EDAC (1.4 g, 7.30 mmol). The mixture was then stirred at room temperature for 2 hours. TLC indicated the complete consumption of the acid. Water was then added to quench the reaction and to precipitate out the product. Cinnamide was then collected through filtration and washed with cold water. The light yellow product was dried in a vacuum oven overnight at 40 °C to give 2.04 g (6.03 mmol, 91.6 %) of the title compound.

Example 32B

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

To a stirred solution of 4-chloro-3-nitro-cinnamide (275 mg, 0.814 mmol) from Example 32A in 1.0 mL of DMF was added potassium carbonate (169 mg, 1.22 mmol),

followed by the dropwise addition of 2,4-dichlorothiophenol (146 mg, 0.815 mmol). The mixture was then stirred at room temperature for 60 minutes. Completion of the reaction was indicated by the TLC. Water was then added to precipitate the product. Filtration, washing with cold water, and drying in a vacuum oven afforded 350 mg (0.728 mmol, 89%) of the title compound as a light yellow solid. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 2.05 (s, 3H), 3.42-3.50 (br m, 4H), 3.50-3.64 (br m, 2H), 3.64-3.79 (br m, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 15.3 Hz, 1H), 7.55 (d, *J* = 15.3 Hz, 1H), 7.63 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 8.69 (d, *J* = 1.8 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 497, 499, 501. Analysis calculated for $C_{21}H_{19}N_3O_4Cl_2S_1$ 0.82H_2O: C, 50.94; H, 4.20; N, 8.49. Found: C, 50.91; H, 4.21; N, 8.69.

A18

Example 33

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl) ethenyl)phenyl] sulfide

The crude product was purified with Gilson HPLC system, YMC C-18 column, 75x30 mm I.D., S-5 μM, 120 Å, and a flow rate of 25 mL/min, λ=214, 245 nm; mobile phase A, 0.05 M NH_4Oac, and B, CH_3CN; linear gradient 20-100% of B in 20 minutes to give the title compound (24 mg, 67%) as a light-yellow powder; ^{1}H NMR (d^6-DMSO, 300 MHz) δ 1.64 (p, *J* = 7.1 Hz, 2H), 1.91 (p, *J* = 7.5 Hz, 2H), 2.21 (t, *J* = 8.3 Hz, 2H), 3.15 (q, *J* = 6.3 Hz, 2H), 3.21 (dd, *J* = 9.9, 17.7 Hz, 2H), 3.32 (overlapping t, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 15.6 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 2.4, 8.1 Hz, 1H), 7.79 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.84 (d, *J* = 8.7 Hz,

A18

1H), 7.96 (d, J = 2.4 Hz, 1H), 8.18 (t, J = 6.0 Hz, 1H), 8.46 (d, J = 2.1 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 494, 496.

Beginning on page 114, line 7 and ending on page 114, line 19:

To a stirred solution of piperazine TFA salt (35 mg, 0.067 mmol) from Example 38A in 2.0 mL of CH_2Cl_2 was added Et_3N (23 μL, 0.17 mmol), 4-dimethylaminopyridine (DMAP) (1.0 mg, 0.0082 mmol), and furyl chloride (8.0 μL, 0.080 mmol). The mixture was then stirred at room temperature for 30 minutes before the solvent was removed. The crude product was purified with Gilson HPLC system, YMC C-18 column, 75x30 mm I.D., S-5 μM, 120 Å, and a flow rate of 25 mL/min, λ=214, 245 nm; mobile phase A, 0.05 M NH_4OAc, and B, CH_3CN; linear gradient 20-100% of B in 20 minutes to give the title compound (24 mg, 67%) as a light-yellow powder; ^1H NMR (d^6-DMSO, 300 MHz) δ 3.62-3.87 (br m, 8H), 6.66 (q, J = 2.1 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 7.04 (d, J = 3.3 Hz, 1H), 7.44 (d, J = 15.3 Hz, 1H), 7.56 (d, J = 15.3 Hz, 1H), 7.63 (dd, J = 2.4, 8.1 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.92 (dd, J = 2.1, 12.0 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 8.70 (d, J = 2.1 Hz, 1H). MS (APCI) $(M+H)^+$ at *m/z* 532, 534, 536.

A19

Beginning on page 117, line 13 and ending on page 117, line 22:

To a stirred solution of the ethyl ester (40 mg, 0.074 mmol) from Example 43A in 2 mL of ethanol was added saturated LiOH (0.25 mL). The mixture was then stirred at room temperature for 2 hours. Water (2 mL) was then added to the reaction mixture, which was then acidified to pH = 2 with concentrated HCl. The precipitates were collected through filtration, washed with cold water, dried under vacuum to give the title

A20

A20

compound (30 mg, 79%) as a light yellow solid. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 3.52 (br m, 4H), 3.62 (br m, 2H), 3.76 (br m, 2H), 6.84 (d, *J* = 9.0 Hz, 1H), 7.46 (d, *J* = 15.3 Hz,1H), 7.56 (d, *J* = 15.3 Hz, 1H), 7.63 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 8.70 (br d, 1H). MS (APCI) (M-COO)$^+$ at *m/z* 466, 468, 470.

Beginning on page 123, line 7 and ending on page 123, line 12:

A21

A mixture of the cinnamate (500 mg, 1.37 mmol) from Example 52B in 5 mL of EtOH/THF (4:1) was stirred with sat. LiOH solution (0.50 mL) at 50 °C for 2 hours. The mixture was then acidified with 3N HCl and extracted with CH_2Cl_2 (3x10 mL). The combined organic layer was dried over $MgSO_4$, concentrated under reduced pressure to give the title compound (450mg, 97%) as a white solid.

Beginning on page 124, line 21, and ending on page 125, line 8:

A22

To a stirred solution of morpholine (10 μL, 0.11 mmol) in 0.5 mL of CH_3CN was added Hunig's base (23.7 μL, 0.14 mmol), followed by the bromide (40 mg, 0.091 mmol). The mixture was then stirred at room temperature for 2 hours. Solvent was then removed and the crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the title compound as a white solid. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 2.33 (br t, 4H), 3.45 (br t, 4H), 3.50-3.65 (m, 6H), 3.56 (s, 2H), 3.65-3.80 (br m, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 15.3 Hz, 1H), 7.35-7.41 (m, 2H), 7.43 (d, *J* = 15.3 Hz, 1H), 7.46 (td, *J* = 2.4, 8.1 Hz, 1H), 7.52 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH_3) (M+H)$^+$ at *m/z* 459, 461.

Beginning on page 125, line 21 and endingon page 126, line 4:

A22

Example 55

(2-(4-(*iso*-Propylaminocarbonylmethyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide

Beginning on page 127, line 4 and ending on page 127, line 14:

A23

To a stirred solution of the alcohol (368 mg, 0.94 mmol) from Example 11 in 5 mL of anhydrous acetonitrile was added activated 4Å molecular sieves, TPAP (3.3 mg, 0.0094 mmol), and NMO (110 mg, 1.03 mmol). The mixture was then stirred at room temperature for 3 hours. The reaction mixture was then quenched with dimethyl sulfide (100 μL). The crude product was filtered through celite, washed with acetonitrile, condensed in vacuo. The title compound was purified by silica gel column chromatography to give a white solid (216 mg, 59 %). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 3.60 (br m, 6H), 3.73 (br m, 2H), 7.00 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 15.3 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 15.3 Hz, 1H), 7.52 (td, J = 1.8, 8.1 Hz, 1H), 7.61 (td, J = 1.8, 8.1 Hz, 1H), 7.71 (dd, J = 2.1, 8.4 Hz, 1H), 8.02 (dd, J = 2.1, 8.4 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H). MS (DCI/NH_3) $(M+H)^+$ at *m/z* 388, 390.

Beginning on page 128, line 8 and ending on page 129, line 2:

A24

A mixture of bromide (80 mg, 0.18 mmol) from Example 12, acryloylmorpholine (33 mg, 0.23 mmol), $Pd(OAc)_2$ (2.0 mg, 0.009 mmol), P(*o*-tolyl)$_3$ (17 mg, 0.056 mmol), Et_3N (39 μL, 0.27 mmol), and anhydrous DMF (1.0 mL) in a pressure tube was flushed with nitrogen for 5 minutes before it was capped and heated at 110 °C overnight. TLC indicated almost complete consumption of the starting bromide. The reaction mixture was

then allowed to cool to room temperature, partitioned between EtOAc and water. The aqueous layer was extracted once with EtOAc. The combined organic layer was washed with water and brine, dried over Na_2SO_4, condensed under reduced pressure. The crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the title compound as a light-brown solid (35 mg, 39%). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 3.43-3.88 (m, 16H), 6.58 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 15.3 Hz, 2H), 7.43 (d, J = 15.3 Hz, 1H), 7.47-7.64 (m, 4H), 7.86 (d, J = 15.3 Hz, 1H), 8.06 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H). MS (DCI/NH_3) $(M+NH_4)^+$ at *m/z* 516, 518. Analysis calculated for $C_{26}H_{27}N_2O_4Cl_1S_1 \cdot 0.46H_2O$: C, 61.56; H, 5.55; N, 5.21. Found: C, 61.56; H, 5.50; N, 5.43.

A24

Beginning on page 129, line 19 and ending on page 130, line 5:

A mixture of the aldehyde (20 mg, 0.052 mmol) from Example 57, 1,1-dimethyl hydrazine (3.9 μL, 0.052 mmol) in 0.5 mL of EtOH with a tiny amount of AcOH was stirred at room temperature overnight. The solvent was then removed and the product was purified by preparative TLC to give the title compound (20 mg, 90%) as a white solid.

A25

Beginning on page 130, line 10 and ending on page 132, line 14:

Example 62

(2-((3-(1-Morpholinyl)propyl)-1-amino)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide

A26

A mixture of bromide (60 mg, 0.14 mmol) from Example 12, aminopropylmorpholine (24 μL, 0.17 mmol), $Pd_2(dba)_3$ (1.2 mg, 0.0013mmol), BINAP (2.5 mg, 0.004 mmol), NaO*t*-Bu (19 mg, 0.20 mmol), 18-crown-6 (50 mg, 0.20 mmol), and anhydrous toluene (1 mL) in a pressure tube was flushed with nitrogen for 3 minutes

before it was capped and heated at 80 °C overnight. The reaction was then stopped, and allowed to cool to room temperature. The reaction mixture was partitioned between EtOAc and water, and the aqueous layer was extracted once with EtOAc. The combined organic layer was then washed with water and brine, dried over Na_2SO_4, condensed under reduced pressure. The crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the title compound as a light-brown oil (30 mg, 44%). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 1.62 (quintet, J = 6.5 Hz, 2H), 2.15-2.26 (m, 8H), 3.17 (q, J = 6.5 Hz, 2H), 3.22-3.76 (m, 12 H), 3.50 (t, J = 6.5 Hz, 2H), 5.72 (t, J = 5.7 Hz, 1H), 6.47 (d, J = 8.7 Hz, 1H), 6.68 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 15.6 Hz, 1H), 7.35-7.42 (m, 2H), 7.43 (d, J = 15.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 2.1 Hz,1H). MS (APCI) $(M+H)^+$ at *m/z* 502, 504.

A26

Example 63

(2,4-Dichlorophenyl)[2-bromo-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl) ethenyl)phenyl] sulfide

A mixture of nitro compound (780 mg, 1.58 mmol) from Example 33, $SnCl_2$ (1.50 g, 7.91 mmol) in 25 mL of anhydrous EtOH was refluxed under nitrogen atmosphere for 90 minutes. The reaction was then allowed to cool to room temperature, quenched with sat. $NaHCO_3$, extracted with EtOAc (2x50 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, condensed in vacuo to give the crude aniline as yellowish brown solid, which was converted to the bromide without purification.

Example 63A

(2,4-Dichlorophenyl)[2-amino-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl)

ethenyl)phenyl] sulfide

A mixture of nitro compound (780 mg, 1.58 mmol) from Example 33, $SnCl_2$ (1.50 g, 7.91 mmol) in 25 mL of anhydrous EtOH was refluxed under nitrogen atmosphere for 90 minutes. The reaction was then allowed to cool to room temperature, quenched with sat. $NaHCO_3$, extracted with EtOAc (2x50 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, condensed in vacuo to give the crude aniline as yellowish brown solid, which was converted to the bromide without purification.

A26

Example 63B

(2,4-Dichlorophenyl)[2-bromo-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl) ethenyl)phenyl] sulfide

To a stirred solution of *t*-butyl nitrite (57 μL, 0.48 mmol), $CuBr_2$ (87 mg, 0.39 mmol) in 2.0 mL of CH_3CN at room temperature was added a solution of aniline from Example 63A (150 mg, 0.323 mmol) in 1.0 mL of CH_3CN. The dark green solution was then heated at 65 °C under nitrogen atmosphere for 90 minutes. The reaction mixture was then allowed to cool to room temperature, partitioned between EtOAc and 3N HCl. The organic layer was then washed with brine, dried over Na_2SO_4, condensed in vacuo. The crude product was then purified with Gilson Preparative HPLC as described in Example 38B to give the title compound as a light-brown solid (50 mg, 29%). Colorless oil; ^1H NMR (d^6-DMSO, 300 MHz) δ 1.63 (quintet, J = 7.2 Hz, 2H), 1.91 (quintet, J = 8.4 Hz, 2H), 2.22 (t, J = 8.4 Hz, 2H), 3.09-3.47 (m, 6H), 6.67 (d, J = 15.3 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 15.3 Hz, 1H), 7.50 (dd, J = 2.4,

A26

8.7 Hz, 1H), 7.57 (dd, J = 2.1, 8.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 8.13 (t, J = 6.0 Hz, 1H). MS (ESI) $(M+H)^+$ at *m/z* 527, 529, 531, 533.

Beginning on page 134, line 7 and ending on page 134, line 20:

To a stirred solution of the compound (105 mg, 0.26 mmol) from Example 65A in 2 mL of THF under nitrogen atmosphere at 0 °C was added *t*-BuOK solution (1.0M, 281 μL, 0.29 mmol). Light orange precipitates appeared immediately. After completion of the addition, the reaction mixture was stirred at room temperature for 1 hour before the solvent was removed on a rotavap under reduced pressure.

A27

The yellow thiolate thus obtained was dissolved in 0.5 mL of DMF, and 2,3-dichlorobenzaldehyde was then added. The mixture was then heated at 80 °C under nitrogen for 2 hours. Reaction was then stopped and the solvent was removed under vacuum. The crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the title compound as a white solid (25 mg, 21%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (s, 3H), 3.48-3.58 (m, 2H), 3.58-3.84 (m, 6H), 6.53 (d, J = 8.7 Hz, 1H), 6.80 (d, J = 15.3 Hz, 1H), 7.19 (dd, J = 1.8, 8.7 Hz, 1H), 7.51-7.62 (m, 2H), 7.60 (d, J = 15.3 Hz, 1H), 7.84 (dd, J = 1.8, 8.4 Hz, 1H), 7.99 (dd, J = 1.8, 8.4 Hz, 1H). MS (APCI) $(M+NH_4)^+$ at *m/z* 480, 482, 484.

Beginning on page 137 line 2 and ending on page 139, line 7:

A28

To a stirred solution of bromide (75 mg, 0.17 mmol) from Example 12 in toluene in a sealed tube was added sequentially pyrrolidine (18.4 mL, 0.22 mmol), $Pd_2(dba)_3$ (3.0 mg, 0.0034mmol), BINAP (6.0 mg, 0.010mmol), followed by NaO*t*-Bu (26 mg, 0.27

mmol). The resulting mixture was then flushed with anhydrous N_2 for 2 minutes before it was capped and heated at 90 °C for 24 hours. The reaction mixture was then allowed to cool to room temperature and partitioned between ethyl acetate and brine. The organic layer was then dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified using Gilson Preparative HPLC as described in Example 38B to give the title compound (40 mg, 55% yield) as a white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.83 (br s, 4H), 3.40 (br s, 4H), 3.56-3.80 (m, 8H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 15.6 Hz, 1H), 6.81 (br t, *J* = 8.4 Hz, 1H), 6.90 (br s, 1H), 7.15 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.18-7.27 (m, 1H), 7.32 (td, *J* = 1.8, 8.4 Hz, 1H), 7.42 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 15.6 Hz, 1H). MS (APCI$^+$) $(M+H)^+$ at *m/z* 429, 431.

A28

Example 70

(2-Methoxyphenyl)-[2-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

The title compound was prepared according to the procedures of Example 1, giving a white solid, m.p. 162-164C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.60-3.78 (m, 8H), 3.84 (s, 3H), 6.72 (d, J=9Hz, 1H), 6.78 (d, J=16Hz, 1H), 6.96-7.04 (m, 2H), 7.16 (dd, J=9Hz, 2Hz, 1H), 7.40-7.46 (, 2H), 7.55 (d, J=2H, 1H), 7.58 (d, J=16Hz, 1H). Anal. Calcd. for $C_{20}H_{20}ClNO_3S$: C, 61.61; H, 5.17; N, 3.59. Found: C, 61.53, H, 5.22; N, 3.50.

Example 71

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carbomethoxypiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide

Example 71A

1- *tert*-Butoxycarbonyl -2-carbomethoxypiperazine

2-Carbomethoxypiperazine was treated with benzyl chloroformate (1.0 eq) in aqueous $NaHCO_3$ to give 1-benzyloxycarbonyl-3-carbomethoxypiperazine. This material was treated with di-*tert*-butyldicarbonate (1.1 eq) and triethylamine (1.0 eq) in THF to produce 1-*tert*-butoxycarbonyl-4-benzyloxycarbonyl-2-carbomethoxypiperazine. Hydrogenation of this compound in methanol using 10% Pd-C gave the title compound after filtration and solvent removal.

A29

Example 71B

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carbomethoxypiperazin-1-yl)carbonyl) ethenyl) phenyl] sulfide

A mixture of (2-isopropylphenyl)[2-nitro-4-*E*-(carboxyethenyl)phenyl] sulfide (prepared according to the procedures of Example 32), the amine from Example 71A (1.0 eq), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (1.0 eq), and diisopropylethylamine (2.0 eq) in DMF was stirred at ambient temperature for 4 hours. Ethyl acetate was added, and the mixture was washed sequentially with 1N HCl, aqueous $NaHCO_3$, and brine. The resultant yellow solid was treated with 1:1 TFA/dichloromethane at ambient temperature to give the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 1.15 (d, J = 6.6 Hz, 6H); 2.52-3.16 (br m, 4H); 3.25-3.47 (m, 1H); 3.60-3.65 (br d, 3H); 3.60, 3.66 (br s, br s, 3H); 6.61-6.67 (br m, 1H); 7.30-7.62 (m, 6H); 7.88-7.93 (br m, 1H); 8.58-8.65 (br m, 1H). MS (APCI) $(M+H)^+$ at m/z 470. Anal calcd for $C_{24}H_{27}N_3S_1O_5$: C, 61.39; H, 5.80; N, 8.95. Found: C, 61.51; H, 5.87; N, 8.68.

Beginning on page 141, line 15 and ending on page 142, line 2:

Example 77

(2-Isopropylphenyl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

A 29

The title compound was prepared according to the procedures of Example 1. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (s, 1H), 7.52(d, 1H, J = 15.4 Hz), 7.43-7.51 (m, 3H), 7.36 (d, 1H, J = 8.8 Hz), 7.22 (m, 1H), 7. 10 (br, 1H), 6.80 (d, 1H, J = 8.4 Hz), 6.44 (d, 1H, J = 15.4 Hz), 3.49 (dq, 1H, $J_1 = J_2 = 6.9$ Hz), 3.40 (m, 4H), 3.31 (dd, 2H, $J_1 = 5.7$ Hz, $J_2 = 12.0$ Hz), 2.44 (t, 2H, J = 8.1 Hz), 2.08 (tt, 2H, $J_1 = J_2 = 7.5$ Hz), 1.74 (m, 2H), 1.18 (d, 6H, J = 6.9 Hz). MS (ESI) *m/z* 491, 513, 981, 1003. Anal. Calcd for $C_{26}H_{29}F_3N_2O_2S$: C, 63.66; H, 5.96; N, 5.71. Found: C,64.00; H, 6.12, N, 5.68.

Beginning on page 144, line 7 and ending on page 144, line 17:

To a stirred solution of bromide from Example 12 (60 mg, 0.14 mmol) in 1 mL of toluene was added 0.5 mL of sat. Na_2CO_3, $Pd(PPh_3)_4$ (8 mg, 0.007 mmol), phenylboronic acid (17 mg, 0.14 mmol). The mixture was flushed with nitrogen and

A 30

heated at 100 °C for 3 hours. The reaction mixture was then allowed to cool to room temperature and partitioned between ethyl acetate and brine. The organic layer was then dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified using Gilson Preparative HPLC as described in Example 38B to give the title compound as a colorless oil (40 mg, 67% yield); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.58-3.86 (m, 8H), 6.77 (d, *J* = 15.6 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.67 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.29-7.40 (m, 3H), 7.40-7.48 (m, 6H), 7.56 (d, *J* = 15.6 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H). MS ($APCI^+$) $(M+H)^+$ at *m/z* 436, 438.

Beginning on page 145, line 1 and ending on page 145, line 12:

A31

To a solution of the compound of Example 32A (40 mg, 0.12 mmol) in 2.5 mL of dimethylformamide was added 3,4-dimethylthiophenol (17 mg, 0.12 mmol), followed by potassium carbonate powder (20 mg, 0.14 mmol). The mixture was heated at 100°C for 20 hours. The solvent was removed using N_2 gas flow. Water (5 mL) was then added to the residue, the resulting precipitate was collected through filtration, washed with cold water, and air dried to give the title compound (42 mg, 81%) as light yellow solid. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 3H), 2.23 (s, 3H), 2.27 (s, 3H), 3.45 (br, m, 2H), 3.63 (br, m, 6H), 6.79 (s, 1H), 6.82 (d, J = 19 Hz, 1H), 7.18 (d, J = 19 Hz, 1H), 7.24 (dd, J = 4, 19 Hz, 1H), 7.27 (s, 1H), 7.34 (d, J = 21 Hz, 1H), 7.56 (d, J = 39 Hz, 1H), 8.32 (d, J = 4 Hz, 1H). MS (APCI) $(M+H)^+$ at m/z 440. FAB High Resolution MS calculated m/z for $C_{23}H_{26}N_3O_4S$ $(M+H)^+$: 440.1644. Observed m/z: 440.1646.

Beginning on page 147, line 21 and ending on page 148, line 7:

A32

Example 88

(2,3-Dimethoxyphenyl)-[2-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide

The title compound was prepared according to the procedures of Example 1, giving a white solid, m.p. 148-150C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.60-3.78 (m, 8H), 3.85 (s, 3H), 3.91 (s, 3H), 6.78 (d, J=16Hz, 1H), 6.86-6.98 (m, 3H), 7.20 (dd, J=9Hz, 2Hz, 1H), 7.54 (d, J=2Hz, 1H), 7.58 (d, J=16Hz, 1H). Anal. Calcd. for $C_{21}H_{22}ClNO_4S$: C, 60.06; H, 5.28; N, 3.33. Found: C, 59.72; H, 5.34; N, 2.97.

Beginning on page 149, line 1 and ending on page 149, line 9:

A31

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with *t*-butyl 1-piperazinecarboxylate, to give a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) d 1.48 (s, 9H), 3.49 (br s, 4H), 3.56-3.78 (m, 4H), 6.89 (d, J = 15.6 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.18-7.35 (m, 3H), 7.49 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 15.6 Hz, 1H), 7.68 (dd, J = 2.1, 8.4 Hz, 1H), 7.85 (br s, 1H). MS (APCI$^-$) $(M+Cl)^-$ at *m/z* 605, 607, 609. Anal. Calcd for $C_{25}H_{26}N_2O_3BrF_3S \cdot 0.03\ H_2O$: C, 52.50; H, 4.59; N, 4.90. Found: C, 52.54; H, 4.71; N, 4.68.

Beginning on page 150, line 12 and ending on page 150, line 22:

A32

To a stirred solution of benzoic acid from Example 92A (40 mg, 0.088 mmol) in 1 mL of anhydrous DMF with HOBT (15 mg, 0.097 mmol) was added EDAC (19 mg, 0.097 mmol), followed by ammonium chloride (large excess). The pH of the solution was adjusted to 6 with addition of triethylamine. The resulting mixture was then stirred at ambient temperature for 6 hours. Water was added to quenched the reaction. The product precipitated out after stirring for 30 minutes, which was then isolated by filtration and dried in a vacuum oven to give a light yellow solid (25 mg, 63% yield). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.43-3.82 (m, 8H), 6.84 (d, J = 8.7 Hz, 1H), 7.43 (d, J = 15.6 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.66 (t, J = 7.65 Hz, 1H), 8.06 (d, J = 7.80 Hz, 1H), 8.12 (s, 2H), 8.67 (d, J = 2.1 Hz, 1H). MS (ESI$^+$) $(M+Na)^+$ at *m/z* 477.

Beginning on page 151, line 5 and ending on page 151, line 6:

A33

To a stirred solution of benzoic acid from Example 92A (255 mg, 0.56 mmol) in 5 mL of anhydrous THF at 0 °C was added in turn Et_3N (102 mL, 0.73 mmol) and ethyl

chloroformate (70 mL, 0.73 mmol). After 60 minutes, the reaction mixture was filtered through celite plug into a stirred solution of $NaBH_4$ in water at 0 °C. The resulting reaction mixture stirred at 0 °C for 2 hours before it was extracted with EtOAc (2×20 mL). The combined organic layers were washed with 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The crude product was purified using Gilson Preparative HPLC as described in Example 38B to give the title compound (80 mg, 32% yield) as a light-yellow solid. ^1H NMR (d^6-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.40-3.79 (m, 8H), 4.56 (s, 2H), 5.38 (br s, 1H), 6.85 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 15.6 Hz, 1H), 7.52 (br s, 3H), 7.57 (br s, 2H), 7.91 (dd, J = 2.1, 8.7 Hz, 1H), 8.66 (d, J = 2.1 Hz, 1H). MS ($APCI^+$) $(M+NH_4)^+$ at *m/z* 459.

A33

Beginning on page 153, line 4 and ending on page 153, line 22:

Example 97

(2-Ethoxyphenyl)-[2-chloro-4-(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

Example 97A

2-Ethoxybenzenethiol

A34

To 7.82g of ethoxybenzene and 7.41g of tetramethylethylenediamine in 75 mL ether, cooled in an ice bath, a solution of 25.6 mL of a 2.5 M n-butyllithium solution in hexane, was added dropwise under a nitrogen atmosphere. The mixture was stirred for 1 hour at room temperature and then cooled to -65 degrees. Sulfur (2.28 g) was added in portions. The mixture was stirred for 3 hours at room temperature and then cooled in ice. $LiAlH_4$ (0.6 g) was added and the mixture was stirred 1 hour at room temperature. The mixture was again cooled in ice while 5 mL water was added dropwise followed by 15% HCl in water. The aqueous phase was separated and washed with ether. The combined

A34

ether layers were washed with HCl, then water. After drying with Na_2SO_4, the ether was evaporated to give 9.66 g of product. NMR analysis showed 70% pure material with 30% of a diaryl sulfide impurity. This mixture was carried forward to the next step.

Example 97B

(2-Ethoxyphenyl)-[2-chloro-4-(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

Beginning on page 160, line 21 and ending on page 163, line 8:

Example 113

(2-Bromophenyl)[2-chloro-4-(E-((3-(5*S*-hydroxymethyl-2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

A35

(2-Bromophenyl)[2-chloro-4-(2-carboxy-E-ethenyl) phenyl]sulfide was prepared by the procedures described in Example 1 substituting 2,4 dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3,4 dichlorobenzaldehyde. 1-(3-aminopropyl)-5-((*S*)-thexyldimethylsilyloxymethyl)-2-pyrrolidinone (0.2818g, 0.8959 mmol) was added to a solution of this cinnamic acid (0.3312g, 0.8959 mmol), 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (0.3435g, 1.79 mmol), and 1-hydroxybenzotriazole hydrate (0.1816g, 1.34 mmol) in DMF (4.0 mL). After stirring for 12 hours, the reaction mixture was diluted with EtOAc (250 mL), extracted with sat. NH_4Cl (1x75 mL), extracted with H_2O (2x75 mL), rinsed with brine (75mL), and dried over Na_2SO_4. The resultant thexyldimethylsilyl alcohol was purified by flash chromatography (EtOAc) on silica gel (.4974 g, 83%). Tetrabutylammonium fluoride (.68 mL of 1.0 M solution in THF) was added dropwise to a solution of this protected

alcohol (0.4544 g, 0.682 mmol) in THF (1.7 mL). After 2 hours, the reaction was diluted with EtOAc (50 mL) and extracted with sat. NH_4Cl (1x25 mL), extracted with H_2O (2x25 mL), rinsed with brine (25mL), and dried over Na_2SO_4. Flash chromatography (EtOAc → 9:1 CH_2Cl_2:MeOH) on silica gel yielded the title compound (.3144g, 88%). ^{1}H-NMR (DMSO-d_6, 300MHz) δ 8.14 (t, *J* = 5.5 Hz, 1H), 7.81 (m, 2H), 7.53 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.44 (dt, *J* = 7.7, 1.5, 1H), 7.40 (dt, *J* = 7.7, 1.8, 1H), 7.39 (d, *J* = 15.6 Hz, 1H), 7.28 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 15.6 Hz, 1H), 4.84 (t, J = 5.1 Hz, 1H), 2.94-3.62 (m, 8H), 1.54-2.29 (m, 6H), MS(APCI) $(M+H)^+$ at m/z 523, 525, 527, 529.

A35

Example 114

(2-Bromophenyl)[2-chloro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4 dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3,4 dichlorobenzaldehyde, and 6-amino-1-hexanol with 1-(3-aminopropyl)- 2-pyrrolidinone. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 8.12 (t, *J* = 5.9 Hz, 1H), 7.81 (m, 2H), 7.52 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.44 (dt, *J* = 7.5, 1.4, 1H), 7.34 (dt, *J* = 7.5, 2.0, 1H), 7.39 (d, *J* = 15.8 Hz, 1H), 7.28 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 15.8 Hz, 1H), 4.02 (d, J = .7 Hz, 1H), 3.29-3.35 (m, 2H), 3.11-3.25 (m, 4H), 2.21 (t, *J* = 8.1 Hz, 1H), 1.94 (m, 2H), 1.64 (m, 2H), MS(APCI) $(M+H)^+$ at m/z 493, 495, 497, 499.

Example 115

(2-Bromophenyl)[2-chloro-4-(*E*-(N-methyl-N-(3-(2-oxopyrrolidin-1-yl)prop-1-yl)amino)carbonyl) ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4 dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3,4 dichlorobenzaldehyde, and 6-amino-1-hexanol with 1-(3-methylaminopropyl)-2-pyrrolidinone. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 8.06 (d, J = 1.5 Hz, 1H), 7.80 (dd, J = 7.7, 1.1 Hz, 1H), 7.64 (dd, J = 8.5, 1.7 Hz, 1H), 7.25-7.46 (m, 5H), 7.04 (d, J =8.1, 1.1, 1H), 3.14-5.30 (m, 6H), 3.14 (s, 1H), 2.91 (s, 2H), 2.19 (m, 2H), 1.92 (m, 2H), 1.68 (m, 2H), MS(APCI) $(M+H)^+$ at m/z 507, 509, 511, 513.

A35

Example 116

(2-[2-Methoxy]ethoxyphenyl)-[2-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide

Beginning on page 167, line 15 and ending on page 169, line 2:

Example126

(2-Bromophenyl)[2-chloro-4-(*E*-((3-(5*S*-acetoxymethyl-2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

A36

To a solution of the compound of Example 113 (0.0466g, 0.0889 mmol) in CH_2Cl_2 (.5 mL) was added triethylamine (0.024 mL, 0.18 mmol) and acetic anhydride (0.0088 mL, 0.0933 mmol). After 12 hours, the reaction was diluted with MeOH (1.5 mL) and purified by preparative HPLC to provide the title compound (.0458 g, 91%). ^{1}H-NMR (DMSO-d_6, 300MHz) δ 8.14 (t, J = 5.7 Hz, 1H), 7.80 (m, 2H), 7.53 (dd, J = 8.5, 1.5 Hz, 1H), 7.45 (dt, J = 7.7, 1.5, 1H), 7.35 (dt, J = 7.7, 1.8, 1H), 7.39 (d, J = 15.6

Hz, 1H), 7.29 (dd, J = 7.7, 1.8 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 15.6 Hz, 1H), 4.20 (dd, J = 11.8, 3.7 Hz, 1H), 4.03 (dd, J = 11.8, 4.0 Hz, 1H), 3.85 (m, 1H), 3.45 (m, 2H), 3.15 (m, 2H), 2.95 (m, 2H), 2.00-2.48 (m, 2H), 2.02 (s, 3H), 1.51-1.82 (m, 2H), MS(APCI) $(M+H)^+$ at m/z 565, 567, 569, 571.

Example 127

(2-Bromophenyl)[2-chloro-4-(E-((3-(5*S*-methoxymethyl-2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

A36

Sodium hydride (0.0088g, 0.22 mmol, 60% dispersion) was added to a solution of the compound of Example 113 (0.0524g, 0.1 mmol) in DMF (0.5 mL). After 15 minutes, iodomethane (0.025 mL, 0.4 mmol) was added and the reaction was stirred for 12 hours. The reaction was diluted with EtOAc (7 mL) and extracted with sat. NH_4Cl (1x2.5 mL), extracted with H_2O (2x2.5 mL), rinsed with brine (2.5mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude products were diluted with MeOH (1.5 mL) and purified by preparative HPLC to provide the title compound (0.0408 g, 74%). ^{1}H-NMR (DMSO-d_6, 300MHz) δ 8.07 (2, 1H), 7.80 (dd, J = 7.9, 1.3 Hz, 1H), 7.64 (dd, J = 8.3, 1.6 Hz, 1H), 7.23-7.46 (m, 5H), 7.04 (d, J = 8.1, 1H), 3.74 (m, 1H), 4.4-3.52 (m, 6H), 3.27 (s, 1.5H), 3.22 (s, 1.5H), 3.14 (s, 1.5H), 2.91 (s, 1.5H), 1.5-2.3 (m, 6H), MS(APCI) $(M+H)^+$ at m/z 551, 553, 555.

Example 128

(2-Bromophenyl)[2-chloro-4-(*E*-((3-(4*R*-hydroxymethyl-2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 170, line 2 and ending on page 170, line 12:

A36

To a stirred solution of aniline from Example 47 (21 mg, 0.049 mmol) in 1 mL of ethanol was added Me_2SO_4 (14.0 mL, 0.15 mmol) followed by sat. Na_2CO_3 (25 mL). The mixture was then refluxed for one day. The reaction mixture was allowed to cool to ambient temperature, partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was then purified on a Gilson Preparative HPLC as described in Example 38B to give the title compound (10 mg, 45% yield), as a light yellow solid.

Beginning on page 173, line 14 and ending on page 174, line 2:

Example 137

(2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(3-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl) phenyl]sulfide

A37

Beginning on page 177, line 4 and ending on page 178, line 5:

Example 144

(2-Chloro-4,5-diaminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

A38

Example 144A

(2-Chloro-4-nitro, 5-aminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 65B substituting 2,3-dichlorobenzaldehyde with 4,5-dichloro-2-nitroaniline.

A38

Example 144B

(2-Chloro-4,5-diaminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

To a stirred solution of nitrobenzene from Example 144A (170 mg, 0.34 mmol) in 2 mL of EtOH was added $SnCl_2$ (325 mg, 1.72 mmol). The mixture was then refluxed under nitrogen atmosphere for 2 hours. The reaction was allowed to cool to ambient temperature, quenched with sat. $NaHCO_3$, extracted with EtOAc(2×20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo. The residue was then purified on Gilson preparative HPLC as described in Example 38B to give the title compound (70 mg, 44% yield) as a light yellow solid. ^1H NMR (d^6-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.42-3.80 (m, 8H), 4.84 (s, 2H), 5.32 (s, 2H), 6.51 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 15.6 Hz, 1H), 7.41 (d, J = 15.6 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H). MS ($APCI^+$) $(M+H)^+$ at *m/z* 465, 467, 469, 471.

Beginning on page 178, line 17 and ending on page 178, line 19:

Example 146

(6-Chloro-2,3-dihydro-1H-benzimidazol-2-one-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

A39

Beginning on page 179, line 18 and ending on page 179, line 20:

Example 148

A40 (2-Hydroxy-4-aminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 182, line 19 and ending on page 183, line 15:

Example 155

(2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide

The compound of Example 137 was hydrolyzed using an excess of aqueous 10% NaOH in methanol, stirring overnight. The reaction mixture was concentrated in vacuo, water was added, and the solution was extracted with ether. The mixture was acidified; the resultant solid was collected by filtration and dried overnight in a vacuum oven, giving a white solid, m.p. 166-171C. ^{1}H-NMR (DMSO 300 MHz) δ 1.17 (t, J=7Hz, 3H), broad peaks totaling 9 protons at 1.32-1.48, 1.51-1.78, 1.90-2.04, 2.25-2.50, 2.80-2.90, 2.95-3.17, 3.45-3.51, 3.95-4.19, 4.41-4.51, 4.06 (q, J=7Hz, 1H), 6.80 (d, J=9Hz, 1H), 7.01 (t, J=7Hz, 1H), 7.15 (d, J=8Hz, 1H), 7.26-7.40 (m, 2H), 7.40-7.48 (m, 1H), 7.51 (dd, J=9Hz, 2Hz, 1H), 7.99 (d, J=9Hz, 1H). Anal. Calcd. for $C_{23}H_{24}ClNO_4S$: C, 61.94; H, 5.42; N, 3.14 . Found: C, 61.75; H, 5.65; N, 3.15. The resultant acid (303 mg, 0.631 mmol) was dissolved in 3 mL MeOH. A KOH solution (38 mg, 0.595 mmol, of 87.6% KOH) in 1 ml MeOH was added. The resulting solution was concentrated in vacuo, and 5 mL ether was added. The mixture was stirred for one hour to form a powder, which was filtered and dried in the vacuum oven at 60C to yield 307 mg of a solid, water soluble product.

A41

Please delete the paragraph beginning on page 183, line 17 and ending on page 184, line 11.

Beginning on page 184, line 13 and ending on page 184, line 15:

Example 156

A42 (2-Ethoxyphenyl)-[2-chloro-4-(E-[(2-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl) phenyl]sulfide

Beginning on page 185, line 12 and ending on page 185, line 14:

Example 158

A43 (2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(2-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide

Beginning on page 186, line 1 and ending on page 186, line 3:

Example 159

A44 (2-Ethoxyphenyl)[2-trifluoromethyl-4-(E-(((pyrrolidin-3-ene-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 186, line 10 and ending on page 186, line 12:

Example 160

A45 (2-Ethoxyphenyl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 188, line 6 and ending on page 188, line 8:

Example 164

A46 (2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(3-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl) phenyl]sulfide

Beginning on page 188, line 17 and ending on page 188, line 19:

Example 165

A47 (2-Ethoxyphenyl)-[2-chloro-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide

Beginning on page 194, line 6 and ending on page 194, line 8:

Example 177

A48 (2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-(((2-carboxypyrrol-3-ene-1-yl)carbonyl)ethenyl) phenyl] sulfide methyl ester

Beginning on page 195, line 4 and ending on page 195, line 6:

Example 179

A49 (2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-(((2-carboxypyrrol-3-ene-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 198, line 12 and ending on page 198, line 14:

Example 187

A50 (3-[2-Methoxy]ethoxyphenyl)-[2-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide

Beginning on page 199, line 4, and ending on page 201, line 3:

Example 188

A51 (2-Bromophenyl)[2-chloro-4-(E-((4,4'-*S*-dioxythiomorpholin-1-yl)carbonyl) ethenyl)phenyl]sulfide

4-Methylmorpholine *N*-oxide (0.0935 g, 0.798 mmol) and 4Å molecular sieves (0.0333g) were added to a solution of (2-Bromophenyl)[2-chloro-4-(E-

((thiomorpholin-1-yl)carbonyl) ethenyl)phenyl]sulfide (0.1230g, 0.27 mmol; prepared according to the procedures described in Example 1). After 15 minutes, tetrapropylammonium perruthenate (0.0058g, 0.0166 mmol) was added and after 4 hours had elapsed the starting material was consumed by TLC and the crude products were passed through a plug of silica with 5:2 hexane:ethyl acetate→ 9:1 CH_2Cl_2: MeOH. The mixture was then purified by preparative HPLC to provide the title compound (0.0138 g, 10%). ^{1}H-NMR (DMSO-d6, 300MHz) δ 8.12 (d, J = 1.47 Hz, 1H), 7.81 (dd, J = 7.9, 1.3, 2H), 7.65 (dd, J = 8.0, 1.5 Hz, 1H), 7.47 (d, J =9.0 Hz, 1H), 7.27-7.53 (m, 4H), 7.03 (d, J = 9.0 Hz, 1H), 4.12 (br s, 2H), 3.98 (br s, 2H), 3.26 (br s, 2H), 3.19 (br s, 2H), 1.54-2.29 (m, 6H), MS(APCI) $(M+H)^+$ at m/z 486, 488, 490.

AS1

Example 189

(2-Bromophenyl)[2-chloro-4-(E-(N-carbomethoxymethyl-N-(3-(2-oxopyrrolidin-1-yl)prop-1-yl)amino)carbonyl) ethenyl)phenyl]sulfide

Example 189A

N-Carbomethoxymethyl-N-(3-(2-oxopyrrolidin-1-yl)prop-1-yl)amine

Methyl bromoacetate (1.35 mL, 14.3 mmol) was added dropwise to a solution of 3-aminopropyl-2-pyrrolidinone (2.0 mL, 14.3 mmol) and diisopropylethylamine (2.7 mL) in CH_2Cl_2. The reaction was stirred for 12 hours and was then concentrated *in vacuo*, and carried forward without further purification.

Example 189B

(2-Bromophenyl)[2-chloro-4-(E-(N-carbomethoxymethyl-N-(3-(2-oxopyrrolidin-1-yl)prop-1-yl)amino)carbonyl) ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described for Example 113, substituting 2,4 dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3,4 dichlorobenzaldehyde, and 1-(3-aminopropyl)-5-((*S*)-hydroxymethyl)-2-pyrrolidinone with the compound from Example 189A. ^{1}H-NMR (DMSO-d6, 300MHz) δ 8.07 (dd, *J* = 9.4, 1.7 Hz, 1H), 7.81 (m, 1H), 7.64 (m, 1H), 7.24-7.49 (m, 5H), 7.05 (m, 1H), 4.53 (s, 1H), 4.14 (s, 1H), 3.68 (s, 1H), 3.64 (s, 2H), 3.54 (m, 2H), 3.13-3.43 (m, 4H), 2.39 (m, 2H), 1.91 (m, 2H), 1.72 (m, 2H), MS(APCI) $(M+H)^+$ at m/z 565, 567, 569.

AS1

Example 190

(2-Bromophenyl)[2-chloro-4-(E-((4-*S*-oxythiomorpholin-1-yl)carbonyl) ethenyl)phenyl]sulfide

The title compound (0.0178g, 14%) was isolated from the same reaction mixture as described in Example 188. ^{1}H-NMR (DMSO-d6, 300MHz) δ 8.12 (d, *J* = 1.8 Hz, 1H), 7.81 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.65 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.26-7.48 (m, 4H), 7.04 (d, *J* = 7.4 Hz, 1H), 4.29 (br m, 2H), 3.97 (br m, 1H), 3.61 (br m, 1H), 2.80 (br m, 4H), MS(APCI) $(M+H)^+$ at m/z 470, 472, 474.

Beginning on page 202, line 2 and ending on page 202, line 4:

Example 193

AS2

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3,5-dimethyl-4-acetyl-piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 203, line 21 and ending on page 204, line 2:

Example 196

A53 (Benzodioxan-6-yl)[2-nitro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 206, line 1 and ending on page 206, line 12:

A54 Bis-(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (1.20 g, 3.77 mmol), and 18-crown-6 (3.56 g, 13.48 mmol) were dissolved in 22 mL of dry THF. The mixture was cooled to -78 °C and $KN(SiMe_3)_2$ (0.5 M in THF, 4.04 mmol) was added and stirred for 30 minutes. (2-Ethoxyphenyl)[2-trifluoromethyl-4-formyl phenyl] sulfide (1.10 g, 3.77 mmol , prepared according to the procedure of example 1) in 13 mL of THF was added via cannulation. After 1 hour at that temperature, the cooling bath was removed and the mixture allowed to warm to ambient temperature.

Beginning on page 215, line 1 and ending on page 215, line 3:

Example 217

A55 (1-Ethyl-3-(dimethylaminomethyl)indol-7-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 215, line 17 and ending on page 216, line 2:

A56 The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with 6-bromo-5-ethoxybenzodioxane, as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 2.14 (s, 3H), 3.54 (br s, 2H), 3.60-3.88 (m, 6H), 4.06 (q, J = 7.2 Hz, 2H), 4.33 (s, 4H), 6.70 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 15.6 Hz, 1H0, 6.98 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 1.8, 8.4 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H). MS (APCI$^+$) $(M+H)^+$ at *m/z* 503, 505.

Beginning on page 217, line 9 and ending on page 217, line 18:

A57

The title compound was prepared by deprotection of Example 205 with TFA in CH_2Cl_2. The resultant free amine was treated with *tert*-butyl bromoacetate and TEA in acetonitrile at room temperature, and followed by deprotection with TFA in CH_2Cl_2, giving a light solid, mp 120 ^{0}C (dec.). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.20-3.45 (m, 4H), 4.20 (s, 2H), 3.50-3.80 (m, 4H), 4.28-4.46 (m, 4H), 6.86 (d, J=8.5 Hz, 1H), 7.04 (m, J=8.0 Hz, 1H), 7.09 (dd, J=2.0 8.0 Hz, 1H), 7.15 (d, J=2.0 Hz, 1H), 7.40 (d, J=15.5 Hz, 1H), 7.56 (d, J=15.0 Hz, 1H), 7.90 (dd, J=2.0, 8.5 Hz, 1H), 8.63 (m, 1H). MS (ESI) m/z 484 $(M-H)^+$, 486 $(M+H)^+$. Calcd. Anal for $C_{23}H_{21}N_3O_7S \cdot 1.19CF_3COOH \cdot 1.34\ H_2O$: 47.63; H, 4.11; N, 6.89. Found: C, 47.93; H, 4.51; N, 6.49.

Beginning on page 219, line 15 and ending on page 220, line 3

Example 225A

(2-Isopropylphenyl)[2-nitro-4-(*E*-(carboxy)ethenyl) phenyl] sulfide

A58

To a stirred mixture of 4-chloro-3-nitrocinnamic acid (500 mg, 2.2 mmol) in 5 mL of anhydrous DMF with K_2CO_3 (911mg, 6.6 mmol) was added 2-isopropylbenzenethiol (372 mL, 2.2 mmol) in 1 mL of DMF dropwise. The resulting mixture was then heated at 70 °C under nitrogen atmosphere overnight. Water (25 mL) was then added and the reaction mixture was acidified to pH = 4 with 3N HCl. The cloudy mixture was extracted with EtOAc (2×20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo to give the title compound as a viscous light-yellow oil, which was used for coupling with further purification.

Beginning on page 221, line 6 and ending on page 221, line 20:

Example 227

(2-Isopropylphenyl)[2-nitro-4-*(E*-(((3-ethanesulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

A59

To a stirred solution of free acid (50 mg, 0.11 mmol) from Example 226 in 1 mL of methylene chloride was added ethyl sulfonamide (18 mg, 0.17 mmol), EDAC (25 mg, 0.13 mmol), and DAMP (2.7 mg, 0.022 mmol) sequentially. The mixture was stirred at ambient temperature for 16 hours. The solvent was then removed on a rotavap under reduced pressure and the residue was purified on an Alltech sep-pak, eluting with 1% MeOH in EtOAc to give 30 mg (50 % yield) of the title compound as a light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (d, J = 6.3 Hz, 6H), 1.34 (t, J = 7.5 Hz, 3H), 1.61-1.74 (m, 2H), 1.84-2.04 (m, 1H), 2.13-2.35 (m, 1H), 2.60-2.75 (m, 2H), 3.44 (p, J = 7.5 Hz, 2H), 3.53-3.66 (m, 1H), 3.66-3.85 (m, 2H), 4.00-4.18 (m, 1H), 6.71 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 15.6 Hz, 1H), 7.31 (dd, J = 2.4, 8.4 Hz, 1H), 7.41 (d, J = 1.8, 8.4 Hz, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 15.6 Hz, 1H), 8.43 (s, 1H). MS (ESI$^+$) $(M+H)^+$ at *m/z* 546.

Beginning on page 223, line 12 and ending on page 223, line 13:

Example 231

A60

(2-Hydroxyphenyl)-[2-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

A60

Beginning on page 224, line 1 and ending on page 224, line 10:

To a stirred solution of indole compound from Example 85 (35 mg, 0.080 mmol) in 1 mL of anhydrous DMSO was added crushed KOH (18 mg, 0.32 mmol). After 45 minutes, *t*-butyl bromoacetate (23.5 mL, 0.16 mmol) was added. The resulting mixture was stirred at ambient temperature for 10 hours. Water was then added and the reaction mixture was acidified with 3 N HCl to pH = 3. The title compound (25 mg, 63 %) was

A61

collected through filtration and dried in a vacuum oven, giving a white solid. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.38-3.80 (m, 8H), 4.59 (s, 2H), 6.45 (d, J = 3.0 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 7.21 (dd, J = 2.1, 8.7 Hz, 1H), 7.25 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 15.6 Hz, 1H), 7.40 (d, J = 3.0 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.97 (s, 1H). MS (ESI$^+$) $(M-H)^+$ at *m/z* 496, 498.

Beginning on page 224, line 21 and ending on page 225, line 2:

Example 234

A62

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino) carbonyl)ethenyl) phenyl] sulfide

Beginning on page 227, line 21 and ending on page 228, line 2:

Example 240

A63

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 228, line 14 and ending on page 228, line 21:

The title compound was prepared by the procedures described in Example 217, substituting the indole from Example 186 with the indole from Example 85, resulting in a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69-1.80 (m, 2H), 2.08 (p, J = 7.5 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H), 3.27-3.48 (m, 6H), 4.24-4.34 (m, 4H), 6.44 (d, J = 15.6 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 7.01 (dd, J = 2.7, 8.4 Hz, 1H), 7.06 (d,

A64

A64

J = 2.7 Hz, 1H), 7.08 (s, 1H), 7.40 (dd, J = 2.1, 8.4 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.75 (d, J = 2.1 Hz, 1H). MS (ESI^+) $(M+H)^+$ at *m/z* 507.

Beginning on page 231, line 9 and ending on page 231, line 17:

The title compound was prepared by the procedures described in Example 229, substituting the acid from Example 226 with the acid from Example 245, to give a light-yellow solid; ^1H NMR (d^6-DMSO, 300 MHz) δ 1.14 (d, J = 6.9 Hz, 6H), 1.18-1.39 (m,

A65

2H), 1.67-1.79 (m, 2H), 2.39 (s, 3H), 2.60-2.75 (m, 1H), 2.96-3.14 (m, 1H), 3.26-3.42 (m, 1H), 3.34 (septet, J = 6.9 Hz, 1H), 4.10-4.42 (m, 2H), 6.62 (d, J = 8.4 Hz, 1H), 7.32-7.43 (m, 4H), 7.45 (d, J = 15.6 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 3.6 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.87 (dd, J = 2.7, 8.4 Hz, 1H), 8.60 (d, J = 2.7 Hz, 1H). MS (ESI^+) $(M+H)^+$ at *m/z* 606. Anal. Calcd for $C_{31}H_{33}N_3O_6S_2 \cdot 0.26\ H_2O$: C, 60.80; H, 5.52; N, 6.86. Found: C, 60.85; H, 5.84; N, 6.61.

Beginning on page 237, line 4 and ending on page 238, line 5:

To a stirred solution of above-described bromide (1.0 g, 2.12 mmol) in 10 mL of toluene with $Pd(OAc)_2$ (9.5 mg, 0.04 mmol), BINAP (40 mg, 0.06 mmol), and

A66

benzophenone hydrazone (437 mg, 2.12 mmol) was added NaO*t*-Bu (285 mg, 2.97 mmol). The reaction mixture was bubbled with N_2 for 2 minutes before it was heated at 80 °C for 4 hours. The reaction mixture was then allowed to cool to ambient temperature. Ether was then added and the mixture was filtered through celite, washed with diethyl ether. The filtrate was concentrate in vacuo and the residue was purified on a SiO_2 flash

column chromatography eluting with 10-30% EtOAc/hexanes to give 170 mg (13%) of the title compound as a light brown foamy solid.

Example 256C

(2-Methyl-3-(carboethoxymethyl)indol-5-yl)[2-trifluoromethyl-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

A66

To a stirred solution of hydrazone (90 mg, 0.15 mmol) in 2 mL of ethanol was added levunilic acid (24 mL, 23 mmol) and *p*-TsOH (146 mg, 0.75 mmol). The mixture was then refluxed for 2 days. After cooling to ambient temperature, the reaction mixture was partitioned between EtOAc and sat. $NaHCO_3$. The organic layer was then washed with brine, dried over Na_2SO_4, concentrated in vacuo. The residue was then purified on Gilson preparative HPLC as described in Example 38B to give 6.0 mg (7%) of the title compound as a light-brown solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, J = 7.4 Hz, 3H), 2.46 (s, 3H), 3.55-3.83 (br m, 8H), 3.67 (s, 2H), 4.12 (q, J = 7.4 Hz, 2H), 6.79 (d, J = 15.3 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 7.23-7.31 (m, 2H), 7.34 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 15.3 Hz, 1H), 7.76 (s, 1H), 7.80 (s, 1H), 8.04 (s, 1H). MS (ESI^+) $(M+H)^+$ at *m/z* 533.

Beginning on page 242, line 21 and ending on page 243 line 10:

Example 266

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-aza-6,9-dioxaspiro[5.4]decan-1-yl)carbonyl)ethenyl) phenyl] sulfide

A67

The title compound was prepared according to the procedures of Example 1. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.13 (s, 1H), 7.84 (d, 1H, J = 9.0 Hz), 7.48 (d, 1H, J =

15.4 Hz) 7.38 (d, 1H, J = 15.4 Hz), 6.98-7.06 (m, 4H), 4.30 (m, 4H), 3.92 (s, 4H), 3.74 (br, 2H), 2.62 (br, 2H), 1.63 (br, 4H). MS (ESI) *m/z* 508, 1015.

A67

Example 267

(Benzodioxan-6-yl)[2-trifluoro-4-(*E*-((4-(2-oxo-2,3-dihydro-1H-benzimidizol-1-yl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 246, line 14 and ending on page 246, line 16:

A68

Example 274

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-aza-6,9-dioxaspiro[5.4]decan-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 249, line 21 and ending on page 251, line 6:

A69

Example 281

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino) carbonyl)ethenyl) phenyl] sulfide

Example 281A

Triisopropylsilyl(1-methylindol-5-yl) sulfide

To a stirred solution of 5-bromo-*N*-methyl indole (300 mg, 1.43 mmol) in 5 mL of benzene in a sealed tube was added $Pd(PPh_3)_4$ (82 mg, 0.072 mmol), followed by KSTIPS (326 mg, 1.43 mmol). The mixture was flushed with N_2, the tube was capped, and the reaction mixture refluxed for 2 hours. The reaction mixture was then allowed to

cool, partitioned between Et_2O and water. The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo. The residue was purified on a SiO_2 flash column chromatography eluting with 5% EtOAc/hexanes to give 400 mg (88 %) of the title compound as a colorless oil.

Example 281B

3-Chloro-4-((1-methylindol-5-yl)thio) benzaldehyde

To a stirred solution of thiolsilyl ether (1.0 g, 3.13 mmol) in 5 mL of DMF with 3-chloro-4-fluorobenzaldehyde (500 mg, 3.13 mmol) at ambient temperature was added CsF (5.7 mg, 0.38 mmol). The mixture was stirred overnight before it was poured in water and extracted with Et_2O (2×25 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, concentrated in vacuo. The residue was purified on a SiO_2 flash column chromatography eluting with 5-10 % EtOAc/hexanes to give 650 mg (71 %) of the title compound as a white solid.

A69

Example 281C

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino) carbonyl)ethenyl) phenyl] sulfide

Beginning on page 253, line 5 and ending on page 253, line 12:

The title compound was prepared by the procedures described in Example 155, substituting the ethyl nipecotate from Example 137 with ethyl ester from Example 283, and KOH with NaOH, to provide a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45-

A70

A70

1.69 (m, 1H), 1.69-1.98 (m, 2H), 1.98-2.22 (m, 1H), 2.51-2.70 (m, 1H), 3.05-3.47 (m, 1H), 3.80-4.20 (m, 2H), 3.85 (s, 3H), 4.47-4.68 (m, 1H), 6.53 (d, J = 3.0 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 15.3 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 7.14 (d, J = 3.0 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.51 (s, 1H), 7.52 (d, J = 15.3 Hz, 1H), 7.89 (br s, 1H). MS (ESI^+) $(M-H+H)^+$ at *m/z* 453, 455.

Beginning on page 254, line 4 and ending on page 254, line 6:

A71

Example 286

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 257, line 21 and ending on page 258, line 2:

A72

Example 294

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-(tetrazol-5-yl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 260, line 14 and ending on page 260, line 21:

A73

The title compound was prepared by the procedures described in Example 281B, substituting 3-chloro-4-fluorobenzaldehyde with 4-chloro-3-nitrocinnamide, giving a light yellow solid. ^1H NMR ($CDCl_3$, 300 MHz, 3:2 mixture of diastereomers) δ [2.11 (s), 2.15 (s), 3H in total], 3.48-3.83 (m, 8H), 3.83-4.04 (m, 2H), 4.20 (dd, J = 8.4, 11.4 Hz, 1H), 4.26-4.44 (m, 2H), 6.89 (d, J = 5.7 Hz, 1H), 6.92 (s, 1H), 6.97-7.11 (m,

A73

1H), 7.04 (d, J = 15.0 Hz, 1H), 7.14 (d, J = 2.1 Hz, 1H), 7.46 (br d, J = 9.0 Hz, 1H), 7.65 (d, J = 15.0 Hz, 1H), 8.41 (d, J = 2.1 Hz, 1H). MS (ESI^+) $(M+H)^+$ at *m/z* 500.

Beginning on page 261, line 1 and ending on page 261, line 3:

Example 297

A74

(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 261, line 14 and ending on page 261, line 16:

Example 298

A75

(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 262, line 4 and ending on page 263, line 7:

Example 299

(3-Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

A76

Example 299A

3-(Hydroxymethyl)-6-bromo-benzodioxane

To a stirred solution of 5-bromosalicylaldehyde (5.0 g, 24.9 mmol), and epichlorohydrin (5.6 mL, 72.1 mmol) in 20 mL of DMF at 80 °C was added K_2CO_3 slowly in portions. The resulting mixture was then heated at 90 °C for 3 hours. Reaction

was then stopped, water was added, extracted with diethyl ether. The organic extracts were washed with water, brine, dried over Na_2SO_4, concentrated in vacuo. The residue was purified on a SiO_2 flash column chromatography eluting with 15-30 % EtOAc/hexanes to give 2.82 g (44 %) of the title compound as a colorless oil.

A76 To a stirred solution of the aldehyde (2.82 g, 11 mmol) in 35 mL of $CHCl_3$ was added mCPBA (2.27 g, 13 mmol). The mixture was stirred at ambient temperature for 30 minutes and then heated at 50 °C for 2 hours. The reaction was then quenched with aq. $Na_2S_2O_5$, extracted with Et_2O (2×50 mL). The combined organic layer was washed with aq. $NaHCO_3$, brine, dried over Na_2SO_4, concentrated in vacuo to give 2.92 g of crude product which was proceeded to the next step without purification.

To a stirred solution of the above-described crude formate (2.92 g) in 5 mL of THF was added 3N aq. NaOH (3.9 mL, 11.7 mmol). The reaction mixture was then heated at 70 °C for 4 hours. The reaction mixture was then partitioned between EtOAc and water. The organic layer was then washed with brine, dried over Na_2SO_4, concentrated in vacuo to give 2.50 g (93% over two steps) of the title compound.

Beginning on page 263, line 14 and ending on page 263, line 16:

Example 299C

A77 (3-Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 264, line 18 and ending on page 265 line 2:

Example 301

(2-(and 3-)(Aminomethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

A78

Example 301A

(2-(and 3-)(Mesyloxymethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 265, line 11 and ending on page 265, line 20:

Example 301B

(2-(and 3-)(Azidomethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

A79

To a stirred solution suspension of NaN_3 (44 mg, 0.68 mmol) in 1 mL of DMSO was added mesylate (275 mg) in 0.5 mL of DMSO solution. The reaction mixture was then heated at 70 °C for 2 hours, then cooled to room temperature, water was added, extracted with EtOAc (2×10 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, concentrated in vacuo. The residue was purified on a SiO_2 flash column chromatography eluting with 5-10% MeOH/EtOAc to give 35 mg (17%, two steps) mg of the title compound as a light brown oil.

Beginning on page 266, line 1 and ending on page 266, line 13:

Example 301C

(2-(and 3-)(Aminomethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

A80

To a stirred solution of azide (230 mg, 0.41 mmol) in 1 mL of THF was added PPh_3 (118 mg, 0.45 mmol), followed by one drop of water. The mixture was then stirred at room temperature for one hour. The volatile solvent was then removed in vacuo and the crude product was purified using Gilson Preparative HPLC as described in Example 38B to give 25 mg (11%) of the title compound. Light brown oil; ^1H NMR ($CDCl_3$, 300 MHz, 3:2 mixture of diastereomers) δ 1.74 (br m, 2H), 1.96-2.16 (m, 2H), 2.35-2.50 (m, 2H), 3.23-3.47 (m, 6H), 3.92-4.63 (m, 5H), 6.41-6.55 (m, 1H), 6.83-7.10 (m, 3H), 7.36-7.58 (m, 3H), 7.67-7.67 (m, 2H). MS (ESI^+) $(M+H)^+$ at *m/z* 536. Anal. Calcd for $C_{26}H_{28}F_3N_3O_4S$: C, 58.31; H, 5.27; N, 7.85. Found: C, 58.34; H, 5.48; N, 7.78.

Beginning on page 268, line 21 and ending on page 269, line 1-2:

Example 307

A81

(Benzodioxan-6-yl)[2-chloro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 270, line 12 and ending on page 271, line 7:

Example 310

A82

(2-Methoxyphenyl)-[2,3-dichloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide

Example 310A

2,3-Dichloro-4-trifluoromethanesulfonyloxy-benzaldehyde

2,3-Dichloro-4-hydroxy-benzaldehyde (9.10 g, J. Med. Chem. 19 (4), 534, 1994) was dissolved in 45 mL pyridine at room temperature. The solution was placed in an ice bath and immediately, 15.63 g of trifluoromethanesulfonic anhydride was added slowly. [Note: If the pyridine solution is cooled to zero before addition of triflic anhydride the aldehyde crystallizes out and the mixture cannot be stirred.] After the addition was completed the dark mixture was stirred for 1 hour at room temperature. It was then poured into a stirred mixture of ice water, 100 mL of concentrated HCl and ether. [Note: Not everything is soluble in this mixture] The ether layer was separated, dried over sodium sulfate, and the solvent removed. Warm heptane was added to this residue, and any insoluble material was filtered. The solution was concentrated to give 8.74 g (57% yield) of product as an orange oil which solidified in the refrigerator.

A82

Beginning on page 271, line 11 and ending on page 271, line 17:

2,3-Dichloro-4-trifluoromethanesufonyloxy-benzaldehyde (2.50 g) was dissolved in 6 mL acetonitrile. 2-Methoxybenzenethiol (2.55 g of 70% pure material, 50% excess) was added. With cooling 2.50 g diisopropylethylamine was added slowly. The solution was removed from the ice bath, whereon a solid formed. The solution was warmed in a 50C waterbath for 5 minutes. More acetonitrile (5 mL) was added and the mixture was cooled in ice, and then filtered to get 2.047 g of product, m.p. 137-139C.

A83

Beginning on page 271, line 21 and ending on page 272, line 4:

A84

A mixture of 2,3-dichloro-4-(2-methoxyphenylthio)-benzaldehyde (2.03 g), 1.44 g malonic acid, 5 mL pyridine, and 0.100 g piperidine was heated to 115 degrees for 1.5 hours. The mixture was cooled, and ice and HCl were added. The resulting solid was filtered, washed with water and dissolved in tetrahydrofuran. This solution was dried over sodium sulfate, the solvent removed and ether added to give 1.733 g of product, m.p. 187-188C.

Beginning on page 272, line 6 and ending on page 272, line 18:

Example 310D

(2-Methoxyphenyl)-[2,3-dichloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide

A85

The title compound was prepared according to the procedure of Example 1, substituting the cinnamic acid of Example 310C for Example 1B, giving a white solid, m.p. 161-162C. ^{1}H-NMR ($CDCl_3$ 300 MHz) δ 3.83 (s, 3H), 6.55 (d, J=9Hz, 1H), 6.70 (broad d, J=15 Hz, 1H), 6.99-7.05 (m, 2H), 7.26 (d, J=9 Hz, 1H), 7.43-7.50 (m, 2H), 8.07 (broad d, J=15 Hz, 1H) Anal. Calcd. for $C_{20}H_{19}Cl_2NO_3S$: C, 56.61; H, 4.51; N, 3.30. Found: C, 56.75; H, 4.57; N, 2.61.

Example 311

(2-Methoxyphenyl)-[2,3-dimethyl-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide

Beginning on page 276, line 11 and ending on page 276, line 13:

A86

Example 319

(2-Methoxyphenyl)-[2,3-dichloro-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide

Beginning on page 277, line 10 and ending on page 277, line 11:

A87

~~Example 321~~

(2-Methoxyphenyl)-[3-chloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

Beginning on page 279, line 6 and ending on page 279, line 8:

A88

Example 325

(Benzodioxan-6-yl)[2,3-dichloro-4-(E-((3-(2-oxopyrrolidin-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Beginning on page 282, line 15 and ending on page 282, line 17:

A89

Example 331

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((3-(2-oxopyrrolidin-1-yl)propylamino) carbonyl)ethenyl) phenyl] sulfide

Beginning on page 288, line 15 and ending on page 289, line 3:

A90

To a solution of 5-iodoindole (75 g, 0.31 mol) in dry THF (750mL), at -78°C was added sodium hydride (60% in mineral oil, 14.85 g, 0.37 mol) in one portion. The suspension was stirred at -78°C for 1 hour after which iodomethane (28.8 mL, 0.46 mol) was added. The reaction mixture was stirred overnight with a slow elevation of

temperature to room temperature (no more dry ice was added). Ether (600mL) and hexane (1.2L) were added and the mixture was washed with brine (1.6L) and water (1.5L), dried over Na_2SO_4 and filtered. The solution was concentrated and the residual brown solid was recrystallized from hexane to give the title compound (66 g). The impure fraction from the mother liquor was flash chromatographed (8% EtOAc in hexane) to give an additional quantity of desired product (12.5 g, combined yield of 99%). MS (DCI/NH_3) m/e 258 $(M+H)^+$.

A90

Beginning on page 289, line 8 and ending on page 289, line 10:

Potassium hydride (35% in mineral oil, 12.03 g, 0.105 mol) was charged to a 250 mL round-bottom flask and was washed with dry THF (2x50mL). The resultant KH powder was then suspended in dry THF (75 mL), and cooled to 5 °C. Triisopropylsilylthiol (20.0 g, 0.105 mol) was slowly added via syringe over a period of 15 minutes. Vigorous escape of hydrogen gas was observed with addition of the thiol. The suspension was stirred at 5°C for 1 hour and became homogenous. After another hour stirring at room temperature, this solution was cannulated to a THF solution (100mL) containing Example 340A (24.5 g, 95.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (2.2 g, 1.91 mmol). The yellow suspension was stirred at 70°C for 1 hour. After cooling, ether and hexane were added, and the mixture was washed with brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by flash chromatography (silica gel, 3% EtOAc in hexane) to give the title compound (26.7 g, 88%). MS (DCI/NH_3) m/e 320 $(M+H)^+$.

A91

Beginning on page 290, line14 and ending on page 291, line 5:

A 1 L round-bottom flask was charged with Example 340C (48.4 g, 0.2 mol), $Pd_2(dba)_3$ (4.6 g, 5 mmol), $(Tol)_3P$ (4.66 g, 15.2 mmol), and purged with nitrogen. Dry DMF (300 mL), methyl acrylate (51.66 g, 0.6 mol) and triethylamine (84 mL, 0.6 mol) were then added. The reaction mixture was purged with nitrogen and stirred at 100°C (oil bath) for 16 hours. After cooling to room temperature, white crystalline material formed. Ethyl acetate (500 mL) and brine (not saturated, 800 mL) were added, and stirred. The white crystalline material dissolved. A little insoluble black solid (Pd) was filtered off. To the solution was then added, with stirring, saturated NaCl solution (2 L) and hexane (500 mL). The mixture was stirred for 1 hour. The formed yellowish solid was collected by filtration, washed with water (400 mL), acetonitrile (50 mL) and 1:1 ethyl acetate/hexane (500 mL), and dried to give pure desired compound (44.99g, 91%). MS (DCI/NH_3) *m/e* 247 $(M+H)^+$.

A92

Beginning on page 293, line 12 and ending on page 294, line 5:

Example 340H

(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide, sodium salt

A93

To a suspension of Example 340G (11.8 g, 23.6 mmol) in THF (150 mL) was added a solution of lithium hydroxide monohydrate (1.98 g, 47.2 mmol) in H_2O (30 mL). The mixture was stirred at room temperature overnight. Water (120 mL) was added and the formed transparent solution was stirred for another hour before 10% HCl (30 mL) was added. The mixture was concentrated under reduced pressure to about 120 mL. The

formed solid material was collected by filtration, washed with water, acetonitrile, and dried to give a white solid (11.0 g).

A93

10.50 grams of the solid was suspended in methanol (60 mL), and was treated with a solution NaOH (0.859g) in methanol (20 mL). After all of the solid material went into solution, the solvent was removed under reduced pressure. The residual yellow oil was triturated with ether, and dried to give the title compound as a yellow powder (11.33 g, 95%).

Beginning on page 294, line 8 and ending on page 295, line 22:

Example 341

(2-Ethoxyphenyl)-[2,3-dichloro-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide

A94

The title compound was prepared according to the procedures of Example 310, substituting 2-methoxybenzenethiol prepared according to the procedures of Example 97A. ^{1}H-NMR (CD_3OD, 300 MHz) Potassium salt δ 1.20 (t, J=7Hz, 3H), 1.55-1.72 (m, 2H), 1.88-1.98 (m, 2H), 2.32 (m, 1H), 2.88 (t, J=12Hz, 1H), 3.20 (t, J=12 Hz, 1H), 4.05 (q, J=7Hz, 2H), 4.14 (d, J=12 Hz, 1H), 4.48, (d, J= 12 Hz, 1H), 6.64 9d, J=9Hz, 1H), 7.00-7.15 (m, 3H), 7.44-7.50 (m, 2H), 7.56 (d, J=9Hz, 1H), 7.90 (d, J=15 Hz, 1H) Anal. Calcd. for $C_{23}H_{22}KCl_2NO_4S$ 0.5 H_2O: C, 52.37, H, 4.39, N, 2.66. Found: C, 52,23; H, 4.56; N, 2.49.

Example 342

(2-Ethoxyphenyl)-[2,3-dichloro-4-(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide

The title compound was prepared according to the procedures of Example 310, substituting 2-methoxybenzenethiol with 2-ethoxybenzenethiol prepared according to the procedures of Example 97A. ^{1}H-NMR ($CDCl_3$ 300 MHz) δ 1.25 (t, J=7Hz, 3H), 3.55-3.80 (m, 8H), 4.05 (q, J=7Hz, 2H), 6.63 (d, J=9Hz, 1H), 6.71 (d, J=15 Hz, 1H), 6.95-7.03 (m, 2H), 7.26 (d, J=9Hz, 1H), 7.39-7.50 (m, 2H), 7.99 (d, J=15 Hz, 1H) Anal. Calcd. for $C_{21}H_{21}Cl_2NO_3S$: C, 57.54; H, 4.82; N, 3.20. Found: C, 57.55; H, 4.77; N, 3.14.

Example 343

(2-Ethoxyphenyl)-[2,3-dichloro-4-(*E*-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide

A94

The title compound was prepared according to the procedures of Example 310, substituting 2-methoxybenzenethiol with 2-ethoxybenzenethiol prepared according to the procedures of Example 97A. ^{1}H-NMR (CD_3OD 300MHz) δ 1.20 (t, J=7Hz, 3H), broad peaks totaling 9 protons at 1.4-1.95, 2.0-2.14, 2.22-2.35, 2.75-3.134.10-4.34, 4.69-4.76, 4.05 (q, J=7Hz, 2H), 6.64 (d, J=9Hz, 1H), 7.03 (t, J=8Hz, 1H), 7.10 (d, J=9Hz, 1H), 7.22 (d, J=15 Hz, 1H), 7.45-7.50 (m, 2H), 7.62 (d, J=9Hz, 1H), 7.80 (d, J=15 Hz, 1H). The acid (303 mg, 0.63 mmol) was dissolved in 3 mL of methanol. A solution of KOH (0.60 mmol) in 1 mL of methanol was added. The resultant solution was stirred for 5 minutes and concentrated in vacuo. Ether (5 mL) was added, and the mixture was stirred for 1 hour. The resultant powder was collected by filtration and dried under vacuum at 60C to give 307 mg of a solid, water-soluble product. Anal. Calcd. for $C_{23}H_{22}KCl_2NO_4S$ 0.5 H_2O; C, 52.37; H, 4.39; N, 2.66 . Found: C, 52.20; H, 4.65, N, 3.04.

Beginning on page 299, line 6 and ending on page 299, line 12:

Chloroform (6.7g, 2.0 eq.) was added dropwise to a stirred mixture of $Ca(OH)_2$ (8.95g, 120 mmol.), K_2CO_3 (13.5g, 98 mmol.), 2-chloro-3-(trifluoromethyl)phenol (5.0g, 22 mmol.), and H_2O (50 mL) at 60°-70° over 2 hours. The reaction mixture was cooled, and acidified with conc. HCl. The product was extracted into EtOAc and dried over Na_2SO_4. Solvent was evaporated, the crude product was separated and purified through a silica column, eluting with hexane and EtOAc (3:2) to give 580 mg (10%) of the title compound.

Beginning on page 300, line 1 and ending on page 300, line 14:

To the acyl chloride (37 mg, 0.1 mmol) prepared from the compound of Example 351B, as a solution in CH_2Cl_2 was added 1.2 eq. of ethyl isonipecotate and 1.2 eq. of Hunig's base. The mixture was stirred at room temperature for 20 minutes, ~90% of the solvent was removed in vacuo, and the resultant solution was loaded on a silica column to elute with hexane and EtOAc (3:2) to give 51mg (98%) of the title compound. ^{1}H-NMR (CDCl3, 300MHz) δ 1.25 (t, J=7.5Hz, 3H), 1.65-1.78 (m, 2H), 1.92-2.02 (br, 2H), 2.51-2.60 (m, 1H), 2.93-3.24 (br, 2H), 3.82 (s, 3H), 3.88-3.96 (m,1H), 4.15 (q,J=7.5Hz, 2H), 4.40-4.50 (br, 1H), 6.48 (d, J=15Hz, 1H), 6.72 (d, J=9Hz, 1H), 7.02 (d, J=7.5Hz, 2H), 7.12 (d, J=9Hz, 1H), 7.49 (t, J=9Hz, 2H), 7.86 (qq, J=4.5Hz, 1H). MS (DCI/NH_3) m/e 528 $(M+H)^+$.

Beginning on page 300, line 12 and ending on page 300, line 14:

A96

Example 352

(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Beginning on page 302, line 1 and ending on page 302, line 11:

Example 355

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-(spirohydantoin-5-yl)-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

A97

The title compound was prepared from Example 310C, using the procedures described in Example 340 and substituting methyl isonipecotate with piperidine-4-spiro-5'-hydantoin, which was prepared according to a literature method (Wysong, C., et al, *J. Org. Chem.* **1996**, 7650). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 1.65 (m, 2H), 1.75 (m, 2H), 3.05 (m, 1H), 3.50 (m, 1H), 4,12 (m, 1H), 4.20 (m, 1H), 6.56 (d, J=6.5Hz, 1H), 7.10 (t, J=8.0Hz, 1H), 7.22 (d, J=8.0 Hz, 1H), 7.28 (d, J=15.6 Hz, 1H), 7.49 (dd, J=8.0, 1.7Hz, 1H), 7.56 (t, J=8.2Hz, 1H), 7.76 (d, J=15.6Hz, 1H), 7.84(d, J=8.6Hz, 1H), 8.58 (s, 1H), 10.73(s, 1H). MS (ESI$^-$) *m/z* 504 (M-H)$^-$.

Beginning on page 304, line 8 and ending on page 304, line 18:

A98

Example 359

(Benzodioxan-6-yl)[2,3-bis(trifluoromethyl)-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

Example 359A

1-Methyl-2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene

A98

Hexafluoro-2-butyne (21.0 g, 0.13 mol) was transferred into a reaction bottle and treated with 2-methylfuran (12.86 g, 0.157 mol). This resulting mixture bottle was sealed and heated for 15 hours at 120 °C. After cooling, the excess 2-methylfuran was rotoevaporated in vacuo at room temperature, to give the crude title product (29 g, 92%), which was used directly.

Beginning on page 305, line 1 and ending on page 305, line 5:

A99

A mixture of Example 359A (12.0 g, 0.05 mol) and boron trifluoride-diethyl ether complex (150 mL) was stirred at room temperature overnight, then neutralized carefully with 20% aqueous potassium carbonate, then the mixture was extracted with ether. The ether layer was dried over $MgSO_4$ and evaporated under reduced pressure to afford 10.4g (85%) of the title compound.

Beginning on page 305, line 9 and ending on page 306, line 21:

A100

The phenol compound of Example 359B (10 g, 0.04 mol) was treated with 4-bromobenzenesulfonyl chloride (11.0 g, 0.043 mol) and Hunig's base (5.56 g, 0.043 mol) in CH_2Cl_2 (150 mL). The solution was washed with water, brine and dried over $MgSO_4$. After evaporating the solvent, N-bromosuccinimide (7.3 g, 0.04 mol) and benzoyl peroxide (200 mg) were added and the mixture was suspended in CCl_4 (100mL). The resulting mixture was refluxed for 13 hours. When the reaction was cooled, the white solid was filtered and washed with CCl_4 to afford the crude title compound. This crude product was used for the next step without further purification.

Example 359D

4-Hydroxy-2,3-bis(trifluoromethyl)benzaldehyde

The crude product of Example 359C was dissolved in 60 mL of DMSO and 20 mL of CH_2Cl_2, and 12 g of trimethylamine N-oxide added. The resulting mixture was stirred at rt for 2.5 hours. The reaction mixture was poured into an ice cold 50% saturated aqueous NaCl solution (200 mL) and extracted with ether (3X100 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After evaporation of solvent, the product was purified by column chromatography, eluted with hexane:EtOAc (3:2) to provide 3.0 g of the title compound, plus 4.0 g of recovered 4-[4-bromobenzenesulfonyloxy-2,3-bis(trifluoromethyl)]toluene.

A100

Example 359E

(Benzodioxan-6-yl)-[2,3-bis(trifluoromethyl)-4-(E-carboethenyl)phenyl]sulfide

The title compound was prepared according to the procedures described in Example 330, substituting the compound of Example 359D for 4-hydrox-2,3-dichlorobenzaldehyde.

Example 359F

(Benzodioxan-6-yl)[2,3-bis(trifluoromethyl)-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared from Example 359E by the procedures described in Example 10, giving a white solid. ^{1}H NMR (CD_3OD, 300MHz) δ 1.65(br s, 2H),1.93-2.04 (m, 2H), 2.57-2.65 (m, 1H), 2.95-3.05 (m, 1H), 3.25 (m, 1H), 4.12 (m, 1H), 4.28 (m, 4H), 4.41 (m, 1H), 6.92-7.03 (m, 4H), 7.25 (d, J=9Hz, 1H), 7.72 (d, J=9Hz,

A100

1H), 7.72-7.81 (m, 1H). MS (ESI) *m/e* 562 $(M+H)^+$. Anal calcd for $C_{25}H_{21}NO_5F_6S$: C, 53.48; H, 3.77; N, 2.49. Found: C, 53.42; H, 3.69; N, 2.25.

Beginning on page 307, line 10 and ending on page 307, line 13:

A101

The title compound was prepared by the procedure described in Example 363 using glycine methyl ester as the coupling substrate. HPLC (Supelco C-18 column, water:acetonitrile 50:90- 90:50, 9 minute elution, flow rate 1.5 mL/min, rt = 6.11 minutes MS (APCI) m/e 537 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.46(m, 3H), 1.78(br d, 2H), 2.79(m, 1H), 3.15(m, 1H), 3.62(s, 3H), 3.80(s, 3H), 3.83(d, 2H), 4.20(m, 1H), 4.40(m, 1H), 6.58(d, 1H), 7.09(t, 1H), 7.22(d, 1H), 7.25(dd, 1H), 7.48(d, 1H), 7.56(t, 1H), 7.72(d, 1H), 7.81(d, 1H), 8.28(t, 1H). Anal calcd for $C_{25}H_{26}Cl_2N_2O_5S \cdot 1.3\ H_2O$: C, 53.54; H, 5.14; N, 4.99. Found: C, 53.49; H, 4.88; N, 4.75.

Beginning on page 308, line 5 and ending on page 308, line 10:

A102

The title compound was hydrolyzed as described in Example 340H. HPLC (Supelco C-18 column, water:acetonitrile 90:0- 0:90, 30 minute elution, flow rate 0.8 mL/min) rt 26.14 minutes. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.46 (m, 2H), 1.75 (m, 2H), 2.73 (m, 1H), 3.12 (m, 1H), 3.70 (m, 2H), 3.79 (s, 3H), 4.02 (m, 1H), 4.20 (m, 1H), 4.41 (m, 1H), 6.65 (d, 1H), 7.09 (dt, 1H), 7.22 (d, 1H), 7.25 (dd, 1H), 7.48 (dd, 1H), 7.58 (m, 1H), 7.72 (d, 1H), 7.82 (d, 1H), 8.11 (m, 1H). MS (APCI) *m/e* 523 $(M+H)^+$.

Beginning on page 314, line 3 and ending on page 314, line 5:

A103

Example 369

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(4-tetrahydrofuroylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Beginning on page 314, line 15 and ending on page 314, line 17:

A104

Example 370

(Benzodioxan-6-yl) [2-(benzodioxan-6-sulfanyl)-4-(*E*-((4-morpholino)carbonyl)ethenyl)phenyl] sulfide

Beginning on page 317, line 1 and ending on page 317, line 13:

A105

To a solution of Example 364A (100 mg, 0.24 mmol) and 2-furfural (30 mg, 0.24 mmol) in dichloroethane (2 mL) was added $NaBH(OAc)_3$ (142 mg, 0.67 mmol) under nitrogen atmosphere. The mixture was stirred for 16 hours at room temperature. Dichloromethane (20 mL) was added and the mixture was washed with 5% $NaHCO_3$, then with brine, and the organic phase was separated and concentrated. The residual solid was chromatographed by flash chromatography (5% $MeOH/CH_2CL_2$) and desired fractions were combined, concentrated and dried to afford the title compound as an off-white solid (84 mg, 69%). HPLC (Supelco C-18 column, water:acetonitrile 100:0- 0:100, 15 minute elution, flow rate 1.5 mL/min) rt 11.90 minutes. ^1H NMR (300 MHz, DMSO-d_6) δ 2.39 (m, 4H), 3.52 (s, 2H), 3.55 (m, 2H), 3.63 (m, 2H), 3.79 (s, 3H), 6.29 (d, 1H), 6.40 (m, 1H), 6.57 (d, 1H), 7.08 (dt, 1H), 7.21 (d, 1H), 7.23 (dd, 1H), 7.48 (dd, 1H), 7.57 (m, 2H), 7.72 (d, 1H), 7.80 (d, 1H). MS (ESI) *m/e* 503 $(M+H)^+$.

Beginning on page 323, line 3 and ending on page 323, line 11:

Example 377A (382 mg, 1 mmol) was coupled with (d,l)-ethyl pipecolinate according to the procedure of Example 340G. The derived ethyl ester was hydrolyzed using the method of Example 340H to give 280 mg of the title compound as a light yellow foam (84%). Analytical HPLC: 4.6X250 mm C18 column, 0.8 mL/min, 254 nm, CH_3CN:H_2O with 0.1% TFA, 0:100 (0 minutes), ramp to 90:10 (0-10 minutes), 90:10 (10-18 minutes), ramp to 0:100 (18-20 minutes), rt 11.29 minutes (98.2 area%). ^1H NMR (300 MHz, d6-DMSO) δ 8.07 (t, 1H), 7.65 (dq, 1H), 7.38 (m, 3H), 7.03 (m, 3H), 5.15 (m, 1H), 4.4 (m, 1H), 4.29 (m, 4H), 4.1 (m, 1H), 3.2 (m, 1H), 2.2 (m, 1H), 1.68 (m, 2H), 1.3 (m, 2H). MS (APCI-NH_3) *m/e* 494 $(M+H)^+$, 511 $(M+NH_4)^+$.

A106

Beginning on page 323, line 14 and ending on page 324, line 4:

Example 378

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(((1S,4S)-5-tert-butyloxycarbonyl-2,5-diazabicyclo(2.2.1)heptan-2-yl)carbonyl)ethenyl)phenyl] sulfide

A107

The title compound was prepared by the procedures described in Example 340 substituting methyl isonipecotate with t-butyl (1S,4S)-(-)2,5-diazabicyclo(2.2.1)heptane-2-carboxylate. ^1H NMR (300 MHz, DMSO-d_6) δ 1.40 (s, 9H), 1.82 (m, 2H), 3.17 (m, 1H), 3.30 (m, 2H), 3.58 (m, 1H), 3.82 (s, 3H), 4.05 (m, 1H), 4.40 (m, 1H), 4.75 (br s, 1H), 4.92 (br s, 1H), 6.42 (dd, 1H), 6.58 (d, 1H), 6.75 (d, 1H), 7.05 (d, 1H), 7.35 (d, 1H), 7.50 (d, 1H), 7.65 (d, 1H), 7.68 (d, 1H), 7.78 (t, 1H), 7.77 (s, 1H). MS (ESI^+) *m/z* 558 $(M+H)^+$. Anal calcd for $C_{28}H_{29}N_3Cl_2SO_3$: C, 60.21; H, 5.23; N, 7.52. Found: C, 60.23; H, 5.36; N, 7.41.

Beginning on page 324, line 7 and ending on page 324, line 9:

Example 379

A108 (1-Methylindol-5-yl) [2,3-dichloro-4-(*E/Z*-((1S,4S)-2,5-diazabicyclo(2.2.1)heptan-2-ylcarbonyl)ethenyl)-2,3-dichlorophenyl] sulfide

Beginning on page 325, line 2 and ending on page 325, line 11:

Example 380

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(4-hydroxy-3-carboxypiperidin-1-ylcarbonyl)ethenyl)phenyl] sulfide

A109 To a suspension of Example 340G (300 mg, 0.794 mmol) and methyl 4-oxo-3-piperidine carboxylate hydrochloride (307 mg, 1.59 mmol) in DMF (10 mL) was added EDC (305 mg, 1.59 mmol), HOBt (215 mg, 1.59 mmol) and triethylamine (0.443 mL, 1.59 mmol), HOBt (215 mg, 1.59 mmol) and triethylamine (0.443 mL, 1.59 mmol). The suspension was stirred at room temperature overnight. Ethyl acetate (100 mL) was added and the mixture was washed with brine, water and was concentrated. The residual oil was separated by flash chromatography (60% EtOAc in hexane) to give a white solid (220 mg).

Beginning on page 328, line 11 and ending on page 328, line 20:

A110 To a solution of the resultant compound from Example 340E (12.0 g, 31.7 mmol) in N-methylpyrrolidinone (63 mL) at 0 °C (under dry N_2) was added 3-bromothiophenol (4.0 mL, 7.3 g, 38.8 mmol) and a solution of lithium *tert*-butoxide (3.1

A110

g, 38.8 mmol), and the resulting solution was stirred for 3 hours at 0 °C. The reaction was diluted with 500 mL EtOAc and extracted sequentially with 100 mL water, 3 x 60 mL of 1 N aq. NaOH, then 2 x 100 mL brine. The organic phase was dried over Na_2SO4, filtered, and concentrated in vacuo to produce the crude title compound (9.2 g). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.75 (s, 3H), 6.67 (d, J=15 Hz, 1H), 6.83 (d, J=9 Hz, 1H), 7.46-7.59 (m, 2H), 7.72-7.76 (m, 2H), 7.80 (t, J=2.5 Hz, 1H), 7.85 (d, J=9 Hz, 1H), 7.88 (d, J=15 Hz, 1H); MS (APCI) *m/e* 419 $(M+H)^+$.

Beginning on page 330, line 5 and ending on page 330, line 19:

A111

The procedure of D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722-9723, was adapted. To a stirred solution of Example 384D (180 mg, 0.331 mmol) in ethylene glycol dimethyl ether (1 mL) containing 1-(N,N-dimethylamino)-1'-(dicyclohexylphophino)biphenyl (7 mg, 5 mol%), $Pd_2(dba)_3$ (8 mg, 2.5 mol%), and morpholine (0.058 mL, 0.663 mmol) was added powdered K_3PO_4 (141 mg, 0.663 mmol). The reaction mixture was bubbled with N_2 for 5 minutes and heated at 90 °C in sealed tube for 18 hours. Then the solvent was removed under reduced pressure and residue was diluted with methylene chloride (1 mL). The title compound (90 mg, 50%) was isolated by flash chromatography on silica gel eluting with 20% acetone-hexane. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.18 (t, J=7.5 Hz, 3H), 1.35-1.55 (m, 2H), 1.79-1.91 (m, 2H), 2.58-2.69 (m, 1H), 2.70-2.94 (m, 2H), 3.16 (t, J=4.5 Hz, 2H), 3.15 (t, J=5 Hz, 4H), 3.73 (t, J=4.5 Hz, 4H), 3.78 (t, J=5 Hz, 2H), 4.08 (q, J=7.5 Hz, 2H), 4.11-4.36 (m, 2H), 6.70 (d, J=8.25 Hz, 1H), 6.97 (m, 1H), 7.10-7.27 (m, 2H),7.24 (d, J=15 Hz, 1H), 7.39 (m, 1H), 7.73 (d, J=15 Hz, 1H), 7.86 (d, J=8.25 Hz, 1H); MS (ESI) *m/e* 549, 551 $(M+H)^+$.

Beginning on page 332, line 3 and ending on page 332, line 8:

A112

4-Cyano-4-phenylpiperidine hydrochloride (2.0 g, 0.11 mol) was dissolved in 8 mL of conc. H_2SO_4 and 4mL of H_2O, then the solution was heated at reflux for 4 hours. The solution was cooled and then NaOH was added to precipitate a white solid. The solid was collected, then dissolved in methanol, and the solution was filtered and concentrated to obtain a white solid. This dried solid was used without purification for Example 385B.

Beginning on page 333, line 3 and ending on page 333, line 11:

A113

The methyl ester of the title compound was prepared by the procedures described in Example 356, employing the compound of Example 359D as starting material, to give an oil. The resultant methyl ester was hydrolyzed with aq. NaOH in methanol at 60 °C for 4 hours to give a white solid. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.88 (br t, J=13.5 Hz, 2H), 2.59(br d, J=13.5 Hz, 2H), 3.13(br t, J=13.5 Hz, 1H), 3.75 (s, 3H), 3.44 (br t, J=13.5 Hz, 1H), 4.12 (br d, J=13.5Hz, 1H), 4.42(br d, J=13.5 Hz, 1H), 6.35 (d, J=15 Hz, 1H), 7.0-7.46 (m, 7H), 7.43-7.55 (m, 3H), 7.62-7.85 (m, 2H); MS(ESI) *m/z* 610$(M+H)^+$. Anal calcd for $C_{30}H_{25}F_6NO_4S{\cdot}H_2O$: C, 57.49; H, 4.13; N, 2.20. Found: C, 57.12; H, 3.93; N, 1.77.

Beginning on page 333, line 17 and ending on page 334, line10:

A114

To a suspension of Example 319 (300 mg, 0.64 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (67 μL) and 2 drops of DMF. The yellow suspension was stirred at room temperature for 2 hours to give an orange solution which was then concentrated

under reduced pressure, and dried under vacuum. An aliquot of the resulting acid chloride solution (2 mL) was added to a solution containing o-trimethylsilyloxyamine (101 mg, 0.96 mmol), Hunig's base (122 μL, 0.7 mmol) and DMAP (2 mg) in CH_2Cl_2 (3 mL). After the solution was stirred at room temperature for 1 hour, TBAF (1.0 M solution in THF, 1.5 mL) was then added. The brown solution was stirred at room temperature for another hour, then it was purified by HPLC (Zorbax, C-18) to give the title compound as a white solid (71 mg). ^{1}H NMR (300 MHz, DMSO-d6) δ 1.50 (m, 2H), 1.70 (m, 2H), 2.28 (m, 1H), 2.70 (m, 1H), 3.09 (m, 1H), 3.79 (s, 3H), 4.23 (m, 1H), 4.45 (m, 1H), 6.55 (d, J = 8.8 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 7.25 (m, 2H), 7.48 (d, J = 7.2 Hz, 1H), 7.54 (t, J = 8.2 Hz, 1H), 7.73 (d, J = 15.3 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 8.55 (br s, 1H), 10.46 (s, 1H). MS (ESI^+) *m/z* 481 $(M+H)^+$.

A114

Beginning on page 334, line 16 and ending on page 335, line 4:

The title compound was prepared by the procedures described in Example 1C substituting Example 1B with (2-methoxy) [2,3-dichloro-4-(*E*-(2-carboxyethenyl)phenyl] sulfide and substituting 6-amino-1-hexanol with N-phenylglycine ethyl ester followed by hydrolysis. ^{1}H NMR (300 MHz, DMSO-d6) δ 3.76 (s, 3H), 4.40 (s, 2H), 6.35 (d, J = 15.5 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 7.05 (t, J = 7.3 Hz, 1H), 7.22 (m, 2H), 7.35 (t, J = 7.5 Hz, 3H), 7.44 (t, J = 7.2 Hz, 3H), 7.55 (t, J = 7.4 Hz, 1H), 7.76 (d, J = 15.4 Hz, 1H); MS (ESI^+) *m/z* 488,490 $(M+H)^+$. Anal. calcd for $C_{24}H_{19}NCl_2O_4S$: C, 59.02; H, 3.92; N, 2.87. Found: C, 58.71; H, 4.10; N, 2.58.

A115

Beginning on page 336, line 5 and ending on page 336, line 14:

Allyl bromide (2.0 mL, 22.8 mmol) was added to a stirred solution of Example 388A (6.71 g, 22.8 mmol), cesium carbonate (14.86 g, 45.6 mmol), and DMF (45 mL). After 21 hours, the pale yellow solution was diluted with 1 N aqueous HCl (100 mL) and extracted with Et_2O (2x75 mL). The ether extracts were combined, dried ($MgSO_4$), filtered, and concentrated to a yellow solid (7.20 g, 94%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.28 (s, 1H), 7.58 (dd, *J*=8.4 Hz, *J*=1.7 Hz, 1H), 7.52 (dd, *J*=7.8 Hz, *J*=1.7 Hz, 1H), 7.23 (d, *J*=8.1 Hz, *J*=1.0 Hz, 1H), 7.08 (dt, *J*=7.8 Hz, *J*=1.4 Hz, 1H), 6.82 (d, *J*=1.7 Hz, 1H), 6.52 (d, *J*=1.7 Hz, 1H), 5.97 (m, 1H), 5.33 (d, *J*=17.3 Hz, 1H), 5.28 (d, *J*=10.8 Hz, 1H), 4.61 (m, 2H), 3.80 (s, 3H); MS (APCI) *m/z* 335 $(M+H)^+$.

A116

Beginning on page 338, line 9 and ending on page 338, line 17:

The methyl ester of the title compound was prepared by the procedure described in Example 363 using L-phenylalanine methyl ester as the coupling substrate. The methyl ester was then hydrolyzed as described in Example 340 to provide the title compound. HPLC (Supelco C-18 column, water:acetonitrile 100:0- 0:100, 20 minute elution, flow rate 1.5 mL/min, RT = 13.97 minutes; ^{1}H NMR (300 MHz, DMSO-d6) δ 1.45 (m, 2H), 1.56 (m, 1H), 1.68 (m, 1H), 2.41 (m, 1H), 2.71 (m, 1H), 2.83 (m, 2H), 3.08 (m, 2H), 3.79 (s, 3H), 4.12 (m, 1H), 4.30 (m, 1H), 4.41 (m, 1H), 6.55 (d, 1H), 7.09 (t, 1H), 7.22 (m, 6H), 7.48 (dd, 1H), 7.57 (m, 1H), 7.72 (d, 1H), 7.81 (d, 1H), 8.11 (m, 1H), 12.64 (br s, 1H); MS (ESI) m/e 613 $(M+H)^+$.

A117

Beginning on page 339, line 4 and ending on page 339, line 12:

A118

The methyl ester of the title compound was prepared by the procedure described in Example 363 using L-serine methyl ester as the coupling substrate. The methyl ester was then hydrolyzed as described in Example 340 to give the title compound. HPLC (Supelco C-18 column, water:acetonitrile 100:0- 0:100, 20 minute elution, flow rate 1.5 mL/min, RT = 11.79 minutes ; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48 (m, 2H), 1.72 (m, 2H), 2.55 (m, 2H), 2.71 (m, 1H), 3.10 (m, 1H), 3.62 (m, 2H), 3.79 (s, 3H), 4.22 (m, 2H), 4.41 (m, 1H), 6.55 (d, 1H), 7.09 (t, 1H), 7.34 (m, 2H), 7.48 (m, 1H), 7.57 (m, 1H), 7.71 (d, 1H), 7.81 (d, 1H), 7.96 (br d, 1H); MS (ESI) *m/e* 553 $(M+H)^+$.

Beginning on page 340, line and ending on page , line 4-9:

A119

The title compound (1.2 g, 103%) was prepared from Example 384B (1.00 g, 2.48 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with 1,2,3,6-tetrahydropyridine.

Beginning on page 340, line 15 and ending on page 341, line 2:

A120

The title compound (50 mg, 46%) was prepared by the procedures described in Example 384D, substituting morpholine with ethyl nipecotate. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.17 (t, J=6.8 Hz, 3H), 1.5-1.76 (m, 3H), 1.82-1.95 (m, 1H), 2.06-2.19 (m, 2H), 2.56-2.67 (m, 1H), 2.84-2.96 (m, 1H), 3.06-3.13 (m, 1H), 3.43-3.52 (m, 1H), 3.61-3.74 (m, 2H), 3.99-4.18 (m, 4H), 5.66-5.91 (m, 2H), 6.73 (d, J=9 Hz, 1H), 6.92 (d, J=7.5 Hz, 1H), 7.06-7.12 (m, 2H), 7.31-7.39 (m, 2H), 7.75 (d, J=15 Hz, 1H), 7.80-7.91 (m, 1H); MS (ESI) *m/e* 545, 547 $(M+H)^+$.

Beginning on page 341, line 5 and ending on page341, line 7:

Example 391C

A 121

[3-(3-carboxylpiperidine)] [2,3-dichloro-4-(*E*-[(1,2,3,6-tetrahydropyridin)-1-yl)carbonyl]ethenyl)phenyl] sulfide

Beginning on page 342, line 2 and ending on page 342, line 5:

Example 392

A 122

(3-(4-Pyrrolidin-1-yl)piperidin-1-yl)phenyl) [2,3-dichloro-4-(E-(((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl)ethenyl)phenyl]sulfide

Beginning on page 342, line 7 and ending on page 342, line 9:

~~Example 392A~~

A 123

(3-bromophenyl) [2,3-dichloro-4-(E-(((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl)ethenyl)phenyl]sulfide

Beginning on page 342, line 16 and ending on page 343, line 2:

Example 392B

A 124

(3-(4-Pyrrolidin-1-yl)piperidin-1-yl)phenyl) [2,3-dichloro-4-(E-(((3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl)ethenyl)phenyl]sulfide

Beginning on page 344, line13 and ending on page 344, line 18:

A 125

The title compound (32 mg, 27%) was prepared from Example 393A as described in Example 384D, substituting morpholine with 1,4-dioxa-8-

A 125

azaspiro[4,5]decane. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 1.68 (t, J=5 Hz, 4H), 3.52-3.60 (m, 7H), 3.66 (br s, 2H), 3.91 (s, 4H), 6.71 (d, J=8.75 Hz, 1H), 6.91 (m, 1H), 7.11-7.13 (m, 2H), 7.22 (d, J=15 Hz, 1H), 7.35 (m, 1H), 7.76 (d, J=15 Hz, 1H), 7.85 (d, J=8.75 Hz, 1H); MS (ESI) *m/e* 535, 537 $(M+H)^+$.

Beginning on page 346, line 5 and ending on page 346, line 20:

A solution of Example 4-((2E)-3-{4-[(2-bromophenyl)sulfanyl]-2,3-dichlorophenyl}-2 propenoyl) morpholine (50 mg, 0.11 mmol), tris(benzylidineacetone)dipalladium[0] (5.1 mg, 0.0056 mmol), and tri-*o*-tolylphosphine (11 mg, 0.035 mmol) in 0.2 mL DMF was degassed with nitrogen gas for 10 minutes, then triethylamine (50 μL, 36 mg, 0.36 mmol) and tert-butyl acrylate (50 μL, 44 mg, 0.34 mmol) were added to the solution, and the vessel was sealed under nitrogen and heated in a 100 °C oil bath for 17 hours. The reaction was concentrated under hi-vacuum, and the residue was partially purified by preparative TLC eluting with 10% acetone-CH_2Cl_2 to provide 42 mg (0.080 mmol, 73%) of the title compound as a crude material. The compound was further purified by preparative HPLC (30-100% MeCN in 0.1% aqueous TFA, 40 minute elution, C-18 reverse-phase Sorbax 10 mm column, producing 26 mg (0.051 mmol, 47%) of the title compound as a glass. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.3-2.7 (v br s, 5H), 3.54-3.90 (2 br m, 8H), 6.32 (d, J=16 Hz, 1H), 6.46 (d, J=8 Hz, 1H), 6.69 (br d, J=15 Hz, 1H), 7.24 (br d, partially overlapped with $CHCl_3$, approx. 1H), 7.40-7.54 (m, 2H), 7.59 (dd, J=2,8 Hz, 1H), 7.75 (dd, J=2,8 Hz, 1H), 7.94 (br d, J=15 Hz, 1H), 7.98 (d, J=16 Hz, 1H); MS (ESI) *m/e* 520, 522 $(M+H)^+$.

A 126

Beginning on page 347, line 5 and ending on page 347, line 12:

Example 395A (26 mg, 0.050 mmol) was dissolved in 1 mL chloroform and 1 mL TFA and the solution was stirred at ambient temperature for 1 hour. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55-3.85 (2 br m, 9H), 6.42 (d, J=16 Hz, 1H), 6.47 (d, J=8 Hz, 1H), 6.69 (d, J=15 Hz, 1H), 7.24 (d, partially overlapped with $CHCl_3$, approx. 1H), 7.43-7.56 (m, 2H), 7.78 (dd, J=2,8 Hz, 2H), 7.93 (d, J=15 Hz, 1H), 8.23 (d, J=16 Hz, 1H); MS (ESI) *m/e* 464, 466 $(M+H)^+$.

A 127

Beginning on page 347, line 15 and ending on page 347, line 17:

A 128

Example 396

[3-(4-Carboxylpiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-[(1,2,3,6-tetrahydropyridin-1-yl)carbonyl]ethenyl)phenyl] sulfide

Beginning on page 350, line 17 and ending on page 351, line 11:

A 129

To a solution of *tert*-butyl 1-piperazinecarboxylate (2.5 g. 13.42 mmol) in tetrahydrofuran (21.5 ml, 0.25 M) at 0 °C was added triethylamine (2.25 mL, 16.11 mmol) followed by dimethylsulfamoyl chloride (1.73 mL, 16.11 mmol). The reaction mixture was stirred at 0 °C for 1 hour, diluted with ethyl acetate (100 mL) and washed with saturated $NaHCO_3$ solution (2x30 mL), followed by brine (2x30 mL). The dried (Na_2SO_4) organic layer was evaporated to dryness under reduced pressure and the residue obtained was treated with 10% trifluoroacetic acid in methylene chloride (20 mL) at ambient temperature. After 48 hours, methylene chloride was evaporated in vacuo to obtain a colorless syrup. This crude material was made basic (1 N NaOH, 50 mL), and the mixture was extracted sequentially with ethyl acetate (2x20 mL) and methylene chloride (2x30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated

A 129

to dryness under reduced pressure to obtain the title compound in quantitative yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.77 (s, 3H), 2.79 (s, 3H), 3.12-3.20 (m, 7H), 3.3 (m,1H), 8.86 (br s, 1H); MS (ESI) *m/e* 194 $(M+H)^+$.

Beginning on page 352, line 14 and ending on page 352, line 4:

Ethyl iodide (64 mL, 0.796 mol) was added to furylacrylic acid (100 g, 0.724 mol), diisopropylethyl amine (140 mL, 0.796 mmol), in acetonitrile (1100 mL), and the mixture was heated to 60 °C. After 18 hours, the dark solution was cooled to room temperature and concentrated in vacuo. The resulting brown sludge was diluted with Et_2O (500 mL), washed with 1 N aqueous HCl (2x250 mL), washed with 0.2 N aqueous NaOH (2x250 mL), washed with saturated aqueous $NaHCO_3$ (1x250 mL), dried ($MgSO_4$), filtered, and concentrated to a black oil (114 g, 95%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.84 (d, *J*=1.7 Hz, 1H), 7.46 (d, *J*=15.6 Hz, 1H), 6.97 (d, *J*=3.4 Hz, 1H), 6.33 (dd, *J*=3.4 Hz, *J*=1.7 Hz, 1H), 6.22 (d, *J*=15.9 Hz, 1H), 4.17 (q, *J*=7.1 Hz, 2H), 1.24 (t, *J*=7.1 Hz, 3H); MS (APCI) *m/z* 167 $(M+H)^+$.

NE unclear

Beginning on page 353, line 8 and ending on page 354, line 4:

A solution of Example 401A (20 g, 0.12 mol) in tetrahydrofuran (40 mL) at -50 °C in a 600 mL Parr stirred reactor was treated with hexafluoroacetylene (24.4 g, 0.15 mol), the reactor sealed and heated to 110 °C for 22 hours, allowed to slowly cool to room temperature, and then concentrated to a brown oil (36 g). This oil was then treated with boron trifluoride etherate (33 mL, 0.275 mol) at room temperature for 17 hours, additional boron trifluoride etherate (16 mL, 0.135 mol) added, stirred six hours, cooled to 0 °C , diethyl ether (200 mL) added, followed by slow addition of 150 mL of 2M

A 130

potassium carbonate (vigorous gas evolution). This mixture was diluted with additional diethyl ether, layers separated, organic layer washed with brine, dried ($MgSO_4$) and concentrated to give 39 grams of a brown semi-solid. This semi-solid was diluted with 75 mL of dichloromethane and then flash chromatographed on silica gel with 10-50% ethyl acetate/hexane to provide the title compound (22.8 g, 58%). mp 138-140 °C; ^{1}H NMR (300 MHz, d6 DMSO) δ 11.64 (bs, 1H), 7.95 (d, 1H), 7.78 (dq, 1H), 7.33 (d, 1H), 6.47 (d, 1H), 4.21 (q, 2H), 1.26 (t, 3H); MS (APCI-NH_3) m/e 329 $(M+H)^+$, 346 $(M+NH_4)^+$, 327 $(M-H)^-$. Analytical HPLC: 4.6X250 mm Zorbax C18 column, 1.5 mL/min, 254 nm, CH_3CN:H_2O with 0.1% TFA, 0:100 ramp to 90:10 (0-10 min), 90:10 (10-18 min), ramp to 0:100 (18-20 min), Rt = 10.6 min (98.3 area%).

A 130

Beginning on page 354, line 9 and ending on page 354, line 15:

Triflic anhydride (670 µL, 3.97 mmol) was added to a mixture of Example 401B (1.00 g, 3.05 mmol) and pyridine (6.5 mL). After 2 hours, the dark solution was diluted with Et_2O (75 mL), washed with 1 N aqueous HCl (2x50 mL), washed with saturated aqueous $NaHCO_3$ (1x75 mL), dried ($MgSO_4$), filtered, and concentrated to a dark amber oil (1.35 g, 96%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.33 (d, *J*=8.8 Hz, 1H), 8.11 (d, *J*=8.8 Hz, 1H), 7.87-7.78 (m, 1H), 6.67 (d, *J*=16.0 Hz, 1H), 4.24 (q, *J*=7.1 Hz, 2H), 1.27 (t, *J*=7.1 Hz, 3H); MS (APCI) *m/z* 478 $(M+NH_4)^+$, 495 $(M+Cl)^-$.

A 131

Beginning on page 355, line 5 and ending on page 355, line 16:

2-Methoxythiophenol (524 µL, 4.30 mmol) was added to Example 401C (1.69 g, 3.90 mmol), cesium carbonate (3.18 g, 9.75 mmol), and DMF (8 mL). After 15 hours, the dark solution was diluted with Et_2O (100 mL), washed with water (1x50 mL), washed

A 132

with 1 N aqueous HCl (2x100 mL), washed with saturated aqueous $NaHCO_3$ (1x100 mL), dried ($MgSO_4$), filtered, and concentrated to a dark oil. Flash silica gel column chromatography (85:15 hexane:ethyl acetate) provided the ethyl ester (1.16 g, 66%) as a yellow oil. The ester (858 mg) was subsequently hydrolyzed as previously detailed in Example 155 to provide the title compound (670 mg, 84%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.89 (d, *J*=8.8 Hz, 1H), 7.74-7.67 (m, 1H), 7.55 (dd, *J*=7.5 Hz, *J*=1.7 Hz, 1H), 7.50 (dd, *J*=9.9 Hz, *J*=1.7 Hz, 1H), 7.20 (d, *J*=8.4 Hz, 1H), 7.19 (t, *J*=7.1 Hz, 1H), 7.07 (dt, *J*=7.5 Hz, *J*=1.3 Hz, 1H), 6.44 (d, *J*=15.6 Hz, 1H), 3.75 (s, 3H). MS (APCI) *m/z* 421 ($M-H^+$).

A 132

Beginning on page 359, line 12 and ending on page 360, line 2:

Boron tribromide (84 mL of a 1.0M solution in CH_2Cl_2) was added to a suspension of Example 310C in CH_2Cl_2 (85 mL) at 0 °C. After addition was completed, the ice-water bath was removed, and the homogeneous dark solution was stirred for 2 hours before the mixture was poured into 1 N aqueous HCl (100 mL) and ice (100 g), and extracted with EtOAc (3x100 mL).). The organic layers were combined, washed with brine (1x50 mL), dried ($MgSO_4$), filtered, and concentrated to a white solid (11.3 g). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.26 (s, 1H), 7.82 (d, *J*=15.6, 1H), 7.74 (d, *J*=8.5 Hz, 1H), 7.44 (dt, *J*=7.8 Hz, *J*=1.7 Hz, 1H), 7.41 (dd, *J*=7.4 Hz, *J*=1.7 Hz, 1H), 7.05 (dd, *J*=8.4 Hz, *J*=1.3 Hz, 1H), 6.94 (dt, *J*=7.8 Hz, *J*=1.4 Hz, 1H), 6.52 (d, *J*=8.2 Hz, 1H), 6.50 (d, *J*=16.0 Hz, 1H); MS (APCI) *m/z* 339 $(M-H)^-$, 375 $(M+Cl)^-$.

A 133

Beginning on page 361, line 5 and ending on page 361, line 13:

The title compound was prepared by the procedures described in Example 1C substituting Example 1B with (2-methoxy) [2,3-dichloro-4-(*E*-(2-carboxyethenyl)phenyl] sulfide and substituting 6-amino-1-hexanol with methyl 4-(aminomethyl)benzoate hydrochloride followed by hydrolysis. ^{1}H NMR (300 MHz, DMSO-d_6) δ3.79 (s, 3H), 4.46 (s, 2H), 6.60 (d, J = 8.1 Hz, 1H), 6.66 (d, J = 15.6 Hz, 1H), 7.08 (t, J =8.4 Hz, 1H),

A 134

A 134

7.25 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.51 (m, 3H), 7.75 (d, J = 15.6 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 8.83 (t, J = 5.7 Hz, 1H), 12.90 (brs, 1H); MS (ESI^+) *m/z* 488,490 $(M+H)^+$. Anal. calcd for $C_{24}H_{19}NCl_2O_4S$: C, 59.02; H, 3.92; N, 2.87. Found: C, 58.97; H, 4.07; N, 2.71.

Beginning on page 365, line 4 and ending on page 365, line 7:

A 135

The title compound was constructed according to the procedure for Example 340D and 340E, substituting methyl acrylate with *tert*-butyl acrylate. ^1H NMR (300 MHz, DMSO-d_6) δ 8.11 (d, 1H), 7.78 (d, 1H), 7.72 (d, 1H), 6.72 (d, 1H), 1.5 (s, 9H); MS (APCI-NH_3) *m/e* 456 $(M+Cl)^-$.

Beginning on page 365, line 12 and ending on page 366, line 5:

A 136

Sodium hydride (3.05 g of 60% dispersion, 76 mmol) that had been rinsed with dry tetrahydrofuran (2x), was suspended in 128 mL of THF, cooled to -5 °C, and slowly treated with triisopropylsilyl thiol (12.2 mL, 57 mmol), maintaining an internal temperature below 4 °C, stirred at 0 °C for 1.5 hours, then added to a second flask containing Example 410A (20 g, 47.4 mmol) and tetrakistriphenylphosphine palladium (4.4 g, 3.8 mmol) in 95 mL of THF. The reaction was heated at reflux for 8 hours, then allowed to cool to ambient temperature and concentrated. The resultant slurry was diluted with ethyl acetate, filtered through celite, washed with brine, dried (Na_2SO_4) and concentrated. The resultant black residue was flash chromatographed on silica gel with 2.5-5% acetone/hexane to provide the title compound (18.2 g, 83%).

Beginning on page 367, line 13 and ending on page 368, line 3:

A 137

A solution of Example 410D (2.7 g, 7.29 mmol) in dimethylformamide (32 mL) was treated with hydroxybenzotriazole hydrate (1.2 g, 8.0 mmol), morpholine (1.4 mL, 16 mmol) and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.53 g, 8.0 mmol), stirred at room temperature for 64 hours. The heterogeneous mixture was

A 137

filtered, the white solid washed with water, and then dried in a vacuum oven at 50 °C for 24 hours to provide 2.8 g (88%) of the title compound as a white powder. mp 210-213 °C; ^{1}H NMR (300 MHz, d6 DMSO) δ 8.15 (dd, 1H), 8.03(d, 1H), 7.82 (d, 1H), 7.74 (m, 1H), 7.45 (m, 1H), 7.32 (d, 1H), 7.2 (m, 2H), 3.7 (m, 2H), 3.6 (m, 6H); MS (APCI-NH_3) m/e 440 $(M+H)^+$.

Beginning on page 370, line 5 and ending on page 370, line 17:

A 138

To a solution of Example 411A (107 mg, 0.189 mmol) in CH_2Cl_2 (6 mL) was added mCPBA (80%, 41 mg, 0.189 mmol) at 0 °C. After stirring at the same temperature for 2 hours, THF (2 mL) was added. The solution was concentrated to 1 mL, and was diluted with THF to 3 mL. Lithium hydroxide monohydrate (24 mg) in water (1 mL) was then added. The mixture was stirred at room temperature for 3 hours. The formed transparent solution was separated by HPLC (Zorbax C-18) to give the title compound (68 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.64 (m, 2H), 1.90 (m, 2H), 2.41 (m, 1H), 2.86 (m, 4H), 3.62 (m, 2H), 3.95 (m, 1H), 4.18 (m, 1H), 4.3 (m, 4H), 6.71 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.13 (s, 1H), 7.28 (d, J = 15.3 Hz, 1H), 7.36 (t, J = 8.8 Hz, 1H), 7.80 (d, J = 15.3 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H); MS ($APCI^+$) *m/z* 553,555 $(M+H)^+$. Anal. calcd for $C_{25}H_{26}N_2Cl_2S_2O_4$ 2 TFA: C, 44.57; H, 3.61; N, 3.58. Found: C, 44.34; H, 3.76; N, 3.51.

Beginning on page 371, line 9 and ending on page 372, line 2:

A 139

To a solution of Example 384B (2.35 g, 5.82 mmol) in THF (23 mL) at 5 °C was added *tert*-butyl trichloroacetimidate (2.6 mL, 14.54 mmol) and boron trifluoride-etherate (2.35 mL, 18.54 mmol). The solution was stirred at the same temperature for 10 minutes,

A 139

and was then warmed to room temperature for 5 hours. The yellow solution was poured into aq. $NaHCO_3$ solution, and the mixture was extracted with ethyl acetate. The combined organic phases were washed with water, dried over anhydrous $MgSO_4$, and concentrated. The residual white solid was dissolved in CH_2Cl_2 and was precipitated by adding hexane. The formed suspension was filtered through silica gel, and washed with 1:8 EtOAc/hexane. The solution was concentrated and was further purified by flash chromatography (silica gel, 1:20 EtOAc/hexane) to give the title compound (2.50 g, 94%). MS ($APCI^+$) *m/z* 461 $(M+H)^+$.

Beginning on page 372, line 8 and ending on page 372, line 18:

A 140

A pressure tube was charged with Example 412A (589 mg, 1.28 mmol), $Pd_2(dba)_3$ (30 mg, 0.032 mmol), 2-dicyclohexylphosphanyl-2'-dimethylaminobiphenyl (26 mg, 0.064 mmol), and anhydrous K_3PO_4 (382 mg, 1.8 mmol), and was purged with nitrogen. DME (4 mL) and ethyl isonipecotate (242 mg, 1.54 mmol) were added via syringe, and the mixture was purged with nitrogen again. The red reaction mixture was stirred at room temperature for 0.5 hours and at 95 °C for 15 hours. After the reaction mixture was cooled, it was diluted with ethyl acetate, and washed with brine. The aqueous phase was extracted with ethyl acetate. The combined ethyl acetate solution was concentrated and the residual oil was separated by flash chromatography (silica gel, 1:6 EtOAc/hexane) to give the title compound (523 mg, 76%). MS ($APCI^+$) *m/z* 536 $(M+H)^+$.

Beginning on page 373, line 5 and ending on page 373, line 11:

A 141

To a solution of Example 412B (510 mg, 0.95 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added trifluoroacetic acid (1.6 mL). The yellow solution was stirred at 0 °C for 1

A
147

hour, and was warmed to room temperature for 3 hours. After diluting with CH_2Cl_2, the solution was poured into aq. $NaHCO_3$ solution. The inorganic phase was acidified to pH 5, and was extracted with 10% MeOH in CH_2Cl_2. The combined organic phases were washed with water, concentrated under vacuum and dried to give the title compound (472 mg, 100%). MS ($APCI^+$) *m/z* 480 $(M+H)^+$.

Beginning on page 374, line 1 and ending on page 374, line 15:

A
142

To a suspension of Example 412C (150 mg, 0.31 mmol) in DMF (3 mL) was added 4-hydroxypiperidine (63 mg, 0.62 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodimide (120 mg, 0.62 mmol), HOBt (84 mg, 0.62 mmol) and triethylamine (87 μL, 0.62 mmol) at room temperature. The mixture was stirred at the same temperature for 15 hours. Ethyl acetate was added, the mixture was washed with brine, water, and was concentrated. The residual oil was dissolved in THF (3 mL), and was added lithium hydroxide monohydrate (26 mg, 0.62 mmol) in water (1.5 mL). After stirring for 15 hours, the solution was separated by HPLC (Zorbax C-18) to give the title compound (132 mg, 55%). ^1H NMR (300 MHz, DMSO-d_6) δ 1.32 (m, 2H), 1.65 (m, 2H), 1.75 (m, 2H), 1.92 (m, 2H), 2.43 (m, 1H), 2.86 (t, J = 10.6 Hz, 2H), 3.15 (m, 1H), 3.32 (m, 1H), 3.71 (m, 3H), 3.95 (m, 2H), 6.73 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.13 (s, 1H), 7.24 (d, J = 15.2 Hz, 1H), 7.37 (t, J = 8.1 Hz, 1H), 7.72 (d, J = 15.2 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H); MS (ESI^+) *m/z* 535, 537 $(M+H)^+$. Anal. calcd for $C_{26}H_{28}N_2Cl_2SO_4$ 0.25 TFA: C, 56.43; H, 5.05; N, 4.97. Found: C, 56.37; H, 5.00; N, 4.91.

Beginning on page 375, line 5 to page 376, line 2:

Diethyl azodicarboxylate (270 μL, 1.47 mmol) was added to a suspension of Example 405 (400 mg, 0.95 mmol), triphenylphosphine (386 mg, 1.47 mmol), and THF (2.0 mL). After 16 hours, the dark orange solution was diluted with EtOAc (40 mL), washed with 1 N aqueous HCl (1x20 mL), washed with 0.2 N aqueous NaOH (1x20 mL), washed with brine (1x20 mL), dried ($MgSO_4$), filtered, and concentrated. Flash silica gel column chromatography (9:1 hexane:ethyl acetate) provided a mix of desired ester and triphenyl phosphine oxide. The mixture (200 mg) was combined with lithium hydroxide, monohydrate (34 mg, 0.81 mmol), THF (0.5 mL), and H_2O (0.5 mL). After 21 hours, the cloudy solution was diluted with 0.2 N aqueous NaOH (30 mL), washed with CH_2Cl_2 (2x15 mL), combined with 1 N aqueous HCl until pH<2, and extracted with EtOAc (2x20 mL). The EtOAc extracts were combined, washed with brine (1x20 mL), dried ($MgSO_4$), filtered, and concentrated to a white solid (87 mg, 47%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.80 (d, *J*=7.8, 1H), 7.77 (d, *J*=15.3 Hz, 1H), 7.51 (dt, *J*=8.1 Hz, *J*=2.0 Hz, 1H), 7.48 (d, *J*=8.1 Hz, 1H), 7.22 (d, *J*=15.3 Hz, 1H), 7.09 (d, *J*=7.8 Hz, 1H), 7.08 (dt, *J*=7.1 Hz, *J*=1.0 Hz, 1H), 6.71 (d, *J*=8.9 Hz, 1H), 4.77 (s, 2H), 3.66 (s, 2H), 3.58 (s, 6H); MS (APCI) *m/z* 468 $(M+H)^+$; 466 $(M-H)^-$, 502 $(M+Cl)^-$. Anal. calcd for $C_{21}H_{19}Cl_2NO_5S$: C, 53.85; H, 4.09; N, 2.99. Found: C, 54.07; H, 4.28; N, 2.69.

A 143

Beginning on page 376, line 8 and ending on page 376, line 21:

Ethyl 4-bromobutyrate was added to a mixture of Example 405 (300 mg, 0.731 mmol), cesium carbonate (358 mg, 1.10 mmol), and DMF (1.5 mL). After 16 hours, the pale milky solution was diluted with EtOAc (30 mL), washed with 1 N aqueous HCl (2x25 mL), washed with brine (1x25 mL), dried ($MgSO_4$), filtered, and concentrated to a white solid (326 mg, 85%) as the ethyl ester. The ethyl ester (312 mg, 0.595 mmol), THF

A 144

A 144

(1.5 mL), and H_2O (1.5 mL) were combined with lithium hydroxide, monohydrate (63 mg, 1.50 mmol). After 18 hours, the clear solution was poured into 1 N aqueous HCl (25 mL) and extracted with EtOAc (2x25 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to a white solid (247 mg, 85%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.79 (d, *J*=8.5, 1H), 7.77 (d, *J*=15.6 Hz, 1H), 7.51 (dt, *J*=7.5 Hz, *J*=1.7 Hz, 1H), 7.48 (dd, *J*=7.5 Hz, *J*=1.0 Hz, 1H), 7.20 (d, *J*=14.9 Hz, 1H), 7.19 (d, *J*=9.5 Hz, 1H), 7.06 (t, *J*=7.5 Hz, 1H), 6.63 (d, *J*=8.5 Hz, 1H), 4.01 (t, *J*=6.1 Hz, 2H), 3.65 (s, 2H), 3.58 (s, 6H), 2.10 (t, *J*=7.4 Hz, 2H), 1.75 (m, 2H); MS (APCI) *m/z* 496 $(M+H)^+$.

Beginning on page 386, line 20 and ending on page 387, line 2:

A 145

Example 428

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Beginning on page 387, line 13 and ending on page 387, line 15:

A 146

Example 429

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-((1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Beginning on page 390, line 2 and ending on page 390, line 4:

A 147

Example 433

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bix(trifluoromethyl)-4-(*E*-((bis-(2-ethoxyethyl)amino)carbonyl)ethenyl)phenyl] sulfide

Beginning on page 392, line 16 and ending on page 392, line 18:

A 148

Example 437

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-[(3-(2-oxopyrrolidin-1-yl)propylaminocarbonyl)ethenyl)phenyl] sulfide

Beginning on page 393, line 4 and ending on page393, line 10:

A 149

To a solution of nipecotic acid (10 g, 63.6 mmol) in 1 N NaOH (2.5 g in 64 mL water, 63.6 mmol) at 0 °C was alternately added benzyloxycarbonyl chloride (10.9 mL, 76.5 mmol) in diethyl ether (50 mL) and 1 N NaOH (5 g in 128 mL water, 127.2 mmol) in five portions. The reaction mixture was stirred at 0 °C for 2 hours, and at ambient temperature for 24 hours. Then this was made acidic with 10% HCl and the solid formed was filtered and dried (vacuum oven, 45 °C) to obtain the title compound (18.9 g, 113%). MS (ESI) *m/e* 264 $(M+H)^+$.

Beginning on page 393, line 15 and ending on page 394, line 6:

A 150

A solution of Example A (18 g, 62 mmol) in THF (250 mL, 0.25 M) was treated with trichloroacetimidate (28 mL, 15.5 mmol) and $BF_3 \cdot Et_2O$ (18 mL, 1 mL/g) at ambient temperature. After 18 hours the reaction mixture was quenched with solid $NaHCO_3$ followed by water and stirred vigorously. Then the solvent was removed, and partitioned with ethyl acetate (250 mL). The organic layer was separated and washed with brine (3x80 mL), dried (Na_2SO_4) and evaporated to dryness under reduced pressure to obtain the crude product. The title compound (19.2 g, 96%) was obtained by flash chromatography on silica gel eluting with 20% acetone:hexane. MS (ESI) *m/e* 320 $(M+H)^+$.

Beginning on page 394, line 11 and ending on page 394, line 13:

A 151

Example 437B (19 g,_59.5 mmol) was treated with 10% Pd on carbon (2 g, 10 wt %) in ethanol (237 mL, 0.25 M) to obtain the title compound (10.4 g, 94%).

Beginning on page 394, line 18 and ending on page 395, line 5:

A 152

To a solution of Example 437C (10.4 g, 56.1 mmol) in toluene (112 mL) was added 2-fluoronitrobenzene (6.0 ml, 56 mmol) and CsF (852 mg, 5.6 mmol). The reaction mixture was stirred under reflux conditions for 18 hours, and allowed to cool to ambient temperature. The mixture was diluted with ethyl acetate (100 ml), washed with 10% HCl (2x50 ml), followed by brine (3x100 ml), then dried (Na_2SO_4) and evaporated in vacuo to obtain the title compound (16.5 g, 94%). MS (ESI) *m/e* 307 $(M+H)^+$.

Beginning on page 396, line 1 and ending on page 396, line 11:

A 153

Example 437E was dissolved in 3 N H_2SO_4 (195 mL, 0.25 M), cooled to 0 °C and treated with $NaNO_2$ (3.35 g, 48.6 mmol) in water (20 mL). After 30 minutes at 0 °C potassium iodide (12.01 g, 72.8 mmol) and urea (583 mg, 9.7 mmol) in water (10 mL) were added and stirred for 1 hour. The reaction mixture was quenched with 10% $NaHCO_3$ (50 mL) and partitioned with ethyl acetate (450 mL). The organic layer was separated and washed with 10% $NaHCO_3$ (2x100 mL), brine (2x100mL), dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The title compound (17.2 g, 91%) was obtained by flash chromatography on silica gel eluting with 10% acetone:hexane. ^1H NMR (400 MHz, DMSO-d_6) δ 1.39 (s, 9H),6.85 (tt, J_1=1.5 Hz, J_2=7.5 Hz, 1H), 7.14 (dd, J_1=1.5 Hz, J_2=7.5 Hz, 1H), 7.37 (tt, J_1=1.5 Hz, J_2=7.5 Hz, 1H), 7.84 (dd, J_1=1.5 Hz, J_2=7.5 Hz, 1H); MS (ESI) *m/e* 388 $(M+H)^+$.

Beginning on page 396, line 17 and ending on page 397, line 2:

A 154

Example 437F was converted to the corresponding triisopropylsilyl thiol analogue by the method described for the preparation of Example 340B. Then this intermediate was reacted with Example 340E (2.94 g, 7.75 mmol) at -20 °C as described in Example 340F to obtain the title compound (2.5 g, 63%). MS (ESI) *m/e* 522, 524 $(M+H)^+$.

Beginning on page 397, line 12 and ending on page 397, line 14:

A 155

Example 437I

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-[(3-(2-oxopyrrolidin-1-yl)propylaminocarbonyl)ethenyl)phenyl] sulfide

Beginning on page 398, line 8 and ending on page 398, line 10:

A 156

Example 438

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-[(3-(2-oxopyrrolidin-1-yl)propylamino)carbonyl)ethenyl)phenyl] sulfide

Beginning on page 398, line 16 and ending on page 399, line 2:

A 157

The title compound (445 mg, 71%) was prepared from the reaction of Example 401C (500 mg, 1.08 mmol) with Example 437F, using the procedures described in Example 437G followed by hydrolysis as described in Example 340G. MS (ESI) *m/e* 604 $(M+H)^+$.

Beginning on page 399, line 5 and ending on page 399, line 7:

A 158

Example 438B

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-[(3-(2-oxopyrrolidin-1-yl)propylaminocarbonyl)ethenyl)phenyl] sulfide

Beginning on page 403, line 6 and ending on page 403, line 18:

β-Propiolactone (50 μL, 0.75 mmol) was added to a mixture of Example 405 (308 mg, 0.75 mmol), potassium *tert*-butoxide (750 mL, 1 M in THF), and THF (1.0 mL). After 18 hours, the reaction was diluted with EtOAc, washed with 1 M aqueous HCl, washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by preparative HPLC provided the title compound (72 mg, 20%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.80 (d, *J*=8.4 Hz, 1H), 7.78 (d, *J*=15.8 Hz, 1H), 7.52 (dt, *J*=8.8 Hz, *J*=1.7 Hz, 1H), 7.46 (dd, *J*=7.8 Hz, *J*=17 Hz, 1H), 7.23 (d, *J*=9.1 Hz, 1H), 7.22 (d, *J*=15.3 Hz, 1H), 7.08 (t, *J*=7.4 Hz, 1H), 6.58 (d, *J*=8.5 Hz, 1H), 4.22 (m, 2H), 4.05 (m, 2H), 3.66 (s, 2H), 3.58 (s, 6H); MS (APCI) *m/z* 482 $(M+H)^+$; 480 $(M-H)^-$.

A 159

Beginning on page 404, line 9 and ending on page 405, line 7:

In the biochemical assay, 100 μL of anti-LFA-1 antibody (ICOS Corporation) at a concentration of 5 μg/mL in Dulbecco's phosphate-buffered saline (D-PBS) is used to coat wells of a 96-well microtiter plate overnight at 4°C. The wells are then washed twice with wash buffer (D-PBS w/o Ca^{++} or Mg^{++}, 0.05% Tween 20) and blocked by addition of 200 μL of D-PBS, 5% fish skin gelatin. Recombinant LFA-1 (100 μL of 0.7 μg/mL, ICOS Corporation) in D-PBS is then added to each well. Incubation continues for 1 hour at room temperature and the wells are washed twice with wash buffer. Serial dilutions of compounds being assayed as ICAM-1/LFA-1 antagonists, prepared as 10 mM stock solutions in dimethyl sulfoxide (DMSO), are diluted in D-PBS, 2mM $MgCl_2$, 1% fish skin gelatin and 50 μL of each dilution added to duplicate wells. This is followed by addition of 50 μL of 0.8 μg/mL biotinylated recombinant ICAM-1/Ig (ICOS

A 160

Corporation) to the wells and the plates are incubated at room temperature for 1 hour. The wells are then washed twice with wash buffer and 100 µL of Europium-labeled Streptavidin (Wallac Oy) diluted 1:100 in Delfia assay buffer (Wallac Oy) are added to the wells. Incubation proceeds for 1 hour at room temperature. The wells are washed eight times with wash buffer and 100 µL of enhancement solution (Wallac Oy, cat. No. 1244-105) are added to each well. Incubation proceeds for 5 minutes with constant mixing. Time-resolved fluorimetry measurements are made using the Victor 1420 Multilabel Counter (Wallac Oy) and the percent inhibition of each candidate compound is calculated using the following equation:

Beginning on page 406, line 10 and ending on page 407, line 6:

For measurement of inhibitory activity in the cell-based adhesion assay, 96-well microtiter plates are coated with 70 µL of recombinant ICAM-1/Ig (ICOS Corporation) at a concentration of 5 µg/mL in D-PBS w/o Ca^{++} or Mg^{++} overnight at 4°C. The wells are then washed twice with D-PBS and blocked by addition of 200 µL of D-PBS, 5% fish skin gelatin by incubation for 1 hour at room temperature. Fluorescent tagged JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface; 50 µL at 2×10^6 cells/mL in RPMI 1640/1% fetal bovine serum) are added to the wells. Microtiter plates are incubated for 45 minutes at room temperature and the wells are washed gently once with RPMI-1640/ 1% fetal bovine serum. Fluorescent intensity is measured in a fluorescent plate reader with an excitation wavelength at 485 nM and an emission wavelength at 530 nM. The percent inhibition of a candidate compound at a given concentration is calculated using the following equation:

Beginning on page 407, line 16 to page 408, line 2:

A 162

Compounds of the present invention have been demonstrated to act via interaction with the integrin LFA-1, specifically by binding to the interaction domain (I-domain), which is known to be critical for the adhesion of LFA-1 to a variety of cell adhesion molecules. As such, it is expected that these compounds should block the interaction of LFA-1 with other CAMs. This has in fact been demonstrated for the case of ICAM-3. Compounds of the present invention may be evaluated for their ability to block the adhesion of JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface) to immobilized ICAM-3, as follows:

Beginning on page 410, line 16 and ending on page 411, line 16:

A 163

1. Coat plate (70 µL /well) with 5ug/mL in D-PBS w/ Ca & Mg of ICAM-1/Ig. Cover and incubate overnight at 4°C.
2. Make compound and control dilutions using RPMI-1%FBS and RPMI-50%FBS as the diluents.
3. Decant ICAM-1/Ig coated plate(s), and wash 3X with D-PBS w/o Ca & Mg.
4. Block entire plate(s) with 150 µL /well of Blocking solution. Cover and incubate for approximately 1 hour at room temperature.
5. Count the number of viable JY-8 cells using standard methodology. Need approximately 10-15 x10E6 cells per 96mw tray.

6. Wash cells 1X in RPMI 1640 media without serum - centrifuging for 5 minutes at approximately 1400rpm. Remove supernate and resuspend cell pellet to 5x10E6 cells per mL in RPMI 1640 media without serum.
7. Add 2μL of 1mM Calcein AM for every 1 mL of cell suspension. Mix. Incubate for 30-60 minutes at 37 degrees C in a CO2 incubator (keeping cap of centrifuge tube loose for gas exchange).
8. Add approximately 10 mL of RPMI-1%FBS, aliquot into two equal pools and centrifuge for 5 minutes at 1400rpm.
9. Remove supernate from each pool and resuspend each cell pellet to 2x10E6 cell per mL with RPMI-1%FBS or RPMI-50%FBS.
10. Decant blocked 96mw plate(s) and wash 3X with D-PBS w/o Ca & Mg.
11. Add 50 μL /well of each compound dilution or control. Add 50 μL of Calcein labeled JY-8 cells to all wells. Centrifuge plate(s) briefly (2-5 seconds) at 100-150rpm. Cover and incubate for 30-60 minutes at 37 degrees C.
12. Gently wash wells 1X with approximately 150μL per well of PBS w/Ca & Mg. Remove all liquid from wells.

A 163

Beginning on page 412, line 4 and ending on page 412, line 12:

A 164

The ability of the compounds of this invention to treat arthritis can be demonstrated in a murine collagen-induced arthritis model according to the method of Kakimoto, et al., *Cell Immunol* 142: 326-337, 1992, in a rat collagen-induced arthritis model according to the method of Knoerzer, et al., *Toxicol Pathol* 25:13-19, 1997, in a rat

A 164

adjuvant arthritis model according to the method of Halloran, et al., *Arthritis Rheum* 39: 810-819, 1996, in a rat streptococcal cell wall-induced arthritis model according to the method of Schimmer, et al., *J Immunol* 160: 1466-1477, 1998, or in a SCID-mouse human rheumatoid arthritis model according to the method of Oppenheimer-Marks et al., *J Clin Invest* 101: 1261-1272, 1998.